HARVEY THROUGH JOHN AUBREY'S EYES *

" Ah! my old Friend Dr. Harvey—I knew him right well "

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As we contemplate the past and peer at such reflected images as we can find, how we long for a clear mirror in which to see our chosen heroes moving around in their true colours. Seldom can this wish be gratified for those of our heroes who lived before the reign of Queen Victoria. The 19th century was prolific in full-length portraits of celebrities, many of them as truthful as 19th-century susceptibilities allowed. During the 17th century the art of biography was in its infancy. Izaak Walton's *Lives* of Dr. Donne, George Herbert, Sir Henry Wotton, and the rest immediately spring to the mind as typical examples of the rather casual standards of the period, when artistry mattered more than accuracy (Novarr 1958). Thomas Fuller's *Worthies* (1662) and Anthony Wood's *Athenae Oxonienses* (1691) were biographical dictionaries, serving as quarries for later writers rather than sources of real biography. If we turn to Fuller, we find that beyond coining the pleasant phrase that Harvey's " Father had a week of sons " he gives but little enlightenment. His statement that Harvey " lived a bachelor " undermines our confidence in his accuracy, and in any case there is no attempt to give any sort of picture of the man (Fuller 1662). A few more facts are given by Anthony Wood. A present-day biographer of Harvey must glean the scanty material for the greater part of his life from scattered sources and deduce what he can from hints dropped by Harvey himself in his three extant books.

We are fortunate, however, in possessing one source of intimate details of Harvey's later years, though it was not until 1898 that an Oxford scholar, Andrew Clark, made this source generally available in the two excellent volumes now widely known and valued under the title of *Aubrey's Brief Lives*.†

It is my object today to look with you at William Harvey through John Aubrey's eyes. To do this intelligently it is obviously necessary to look first at Aubrey himself, and in so doing to make acquaintance with one of the oddest and, in some ways, one of the most unsatisfactory characters of the mid and late 17th century. Aubrey was at once industrious and lazy, scholarly and casual, observant but digressive, superstitious and credulous though aiming essentially at the truth. He longed to be a successful writer, but he has only himself to thank for the utter chaos in which most of his writings were left.

John Aubrey

Aubrey was born in 1626 at the hamlet of Easton Pierse in Wiltshire. His father came of a good Herefordshire family—" longævous healthy kindred " Aubrey calls them, though he himself was a sickly child. Later, while at Trinity College, Oxford, he survived an attack of smallpox. Three times in after years he was in danger of being killed by sword-thrust and throughout his life was careless of his health, being fond of good living and especially of drinking with his friends. Nevertheless he lived to the age of 71, being struck down by an apoplexy in his favourite city of Oxford in 1697.

From a worldly point of view his three score years and ten had been largely misspent. He had lived the first part of his life too much under his father's domination, and he was still a young man when his life was disrupted by the civil wars. The death of his father in 1652 allowed him at last to manage, or rather to mismanage, his own affairs, but when he came to think of what he could do he could only answer: " Truly nothing; only Umbrages. If ever I had been good for anything, 'twould have been a Painter, I could fancy a thing so strongly and had so clear an idea of it." But to be a painter meant hard work and that he could not face. So he decided—if indeed he ever decided anything—to be a consistent dilettante. He was attracted by all manner of antiquarian pursuits, he was possessed by an insatiable curiosity, and he was fascinated by the study of his fellow men. And so, in 1654, while in Wales, " he began to enter into pocket memorandum books, philosophical and antiquarian remarques ". It was the filling of pocket memorandum books that was to be his life's work—an insecure basis, it might be thought, for the founding of a reputation as an antiquary and historian, if the memoranda were never to be reduced to order and their contents never made to provide the matter for grave treatises. But whenever he set out to write in an orderly way of what he knew, his mind would run so fast ahead of his pen and be so easily distracted into following side-issues and irrelevancies that the thread was lost and resolution broke down. Consequently his literary output in print was very small, but his disorderly manuscripts were legion. In his own words, he " wanted patience to go through Knotty Studies ", though his industry in recording facts and anecdotes was very great.

Aubrey must have been at once charming and exasperating, as was obviously found by Anthony Wood, the Oxford historian, with whom Aubrey worked. For our present taste in biography Aubrey provides delectable fare—when the chaos of his records has been reduced to order and consistency by the patience of modern scholarship. His style is informal, his language racy, and the very fact that his *Brief Lives* remained unprinted has preserved them in their original and unsophisticated form. He had an unerring instinct for the telling detail. Another of his virtues is his complete lack of self-consciousness or prudery. " I here lay downe to you ", he wrote to Anthony Wood, " the Trueth, and as neer as I can and that religiously as a Poenitent to his Confessor, nothing but the truth: the naked plaine trueth, which is here exposed so bare that the very pudenda are not covered, and affords many passages that would raise a Blush in a young Virgin's cheeke. So that after your perusall, I must desire you to make a Castration and to sowe-on some Figge-leaves—i.e. to be my Index Expurgatorius."

I have drawn attention to this side of Aubrey's work because he has so often been charged with being a false witness. His most illuminating editor, Oliver Lawson Dick (1949), after emphasising the importance of *Aubrey's Lives*, complains that Victorian biographers " made vigorous use of them, usually, from Halliwell-Phillipps to Sir D'Arcy Power, disparaging Aubrey as a gossip as they pilfered his work. And research ", he adds, " since their day has often proved Aubrey, and not his critics, to have been in the right ". This estimate of Aubrey follows a claim that the *Brief Lives* are " of importance if only for the information they give concerning Shakespeare, Milton, Hobbes, and Harvey ".

It will now be evident why I have spent so much time in an attempt to give some indication of what Aubrey is worth as a witness. He was curious, credulous, and unmethodical. It is admitted that he was sometimes inaccurate, but he was never untruthful, a distinction which is of great importance in estimating the value of reportage such as he provides.

* From the Harveian oration delivered on Oct. 17 before the Royal College of Physicians of London.

† An earlier version was published by Dr. Philip Bliss in 1813, but this is inaccurate and incomplete and has been superseded.

Aubrey with Harvey

" Ah! my old Friend Dr. Harvey—I knew him right well." So Aubrey exclaims in his own spontaneous way, and the words are of prime interest to us in this Royal College. Aubrey is the one authority who has left an unvarnished account of our Patron Saint, the only recorder of what he looked like, of what he said, of his personal habits and foibles, and of the manner of his death. Without Aubrey we should be dependent for our knowledge of Harvey on the hints given in his scanty writings and few letters, and on incidental references in the books of the period. No other attempt at word-portraiture of Harvey exists. Can we then believe what Aubrey says? To this question I shall try to provide some sort of an answer.

Aubrey records that he first saw Harvey in 1642 at Oxford after the battle of Edgehill, but adds that he was then " too young to be acquainted with so great a doctor ". It was not until nine years later, in 1651, that he actually became Harvey's friend through a cousin, Lady Mary Montagu, who was also a friend and patient. Aubrey was intending to go to Italy, and in conversation with Harvey took counsel about his journey. Harvey, he says, " was very communicative, and willing to instruct any that were modest and respectfull to him ". Harvey was an experienced traveller and told Aubrey " what to see, what companye to keepe, what Bookes to read, how to manage my Studies. In short he bid me goe to the Fountain Head, and read Aristotle, Cicero, Avicenna "; he then condemned the moderns, or " Neoteriques ", with a very rude word, which Aubrey sets down, but which cannot be repeated here without a fig-leaf.

Aubrey tells how Harvey made him " sitt by him 2 or 3 hours together in his meditating apartment discoursing ". Perhaps they sat in darkness, since Harvey had said that " he did delight to be in the darke, and told me he could then best contemplate ". Aubrey then forms a very just estimate of Harvey's character and of the sources of his greatness.

" He was ", he says, " very far from bigotry. Why, had he been stiffe, starcht, and retired, as other formall Doctors are, he had known no more than they. From the meanest, in some way or other, the learnedst man may learn something. Pride has been one of the greatest stoppers of the Advancement of Learning."

Aubrey's description of Harvey's personal appearance is well known and I need not repeat it here, but it is worth remarking that it agrees with the few authentic portraits that we have. Harvey's forthright character also comes out plainly in the conversation recorded by Aubrey.

" Dr. Harvey told me, and anyone if he examines himself will find it to be true, that a man could not fancy—truthfully—that he is imperfect in any part that he has, *verbi gratiâ*, teeth, Eie, tongue, Spina dorsi, etc. Natura tends to perfection, and in matters of Generation we ought to consult more with our sense and Interest. We see what contemptible products are of the prudent politiques; weake fooles and ricketty children, scandalls to nature and their country. The Heralds are fooles." And so, in conclusion, " A blessing goes with a marriage for love upon a strong impulse ".

Harvey's Religion

We know very little of Harvey's views on matters of religion. He wrote, as Sir D'Arcy Power (1897a) says, " in a broad spirit of religious charity, quite foreign to his environment [that is the intensely religious period in which he lived], but befitting the position he has been called upon to occupy in the history of science ". In the rather conventional phraseology of his last will and testament Harvey humbly rendered his soul " to Him who gave it and to my blessed Lord and Saviour Christ Jesus " (Power 1897b). Sir Charles Scarburgh in his Harveian oration of 1662 said of him " although it was not apparent to all, Harvey always cherished that philosophy which had a reverence for divine authority and uprightness of character so that he might regulate his life with integrity " (Payne 1957). Aubrey was content with saying that he " was a pious good Man ", and we may accept this as the simple truth.

Though curious in all branches of knowledge, Aubrey was no scientist; yet he was particularly struck by Harvey's great interest in comparative anatomy. He was, he says, " the first that I heare of that was curious in Anatomie in England. I remember I heard him say he wrote a booke *De Insectis*, which he had been many yeares about, and had made dissections of Frogges, Toades, and a number of other animals, and had made curious observations on them ". His papers, he added, had been destroyed at the beginning of the Rebellion, and " no griefe was so crucifying to him as the losse of these papers, which for love or money he could never retrieve or obtain ". Aubrey's observation on Harvey's pre-eminence in comparative anatomy in England is perfectly correct. He was in advance of his time and Prof. F. J. Cole (1944) has estimated that he must have examined at least fifty species among the various kinds of animal, both vertebrate and invertebrate. Had more of his work been preserved his fame would be even greater than it is.

Harvey's Latin

As to the manner in which Harvey presented his work, Aubrey raises a doubt concerning his proficiency in the learned tongues. " He understood Greek and Latin very well ", he concedes, " but was no Critique, and he wrote very bad Latin. The *Circuitis Sanguinis* was, as I take it, donne into Latin by Sir George Ent ". I do not know that any scholar has critically examined this suggestion, and I am not competent to do so myself, but even Prof. K. J. Franklin, whose recent translation of *De Motu Cordis* has so delighted the English-speaking medical world, has tacitly accepted the Latin text as Harvey's own; I think it may be assumed that Aubrey's denial of this was wrong. It is significant that Sir George Ent himself, in his preface to *De Generatione*, refers to Harvey's execrable writing, and to having himself assumed the office of proof-reader, but gives no hint that he received the book in English and then translated it into Latin. In this instance Aubrey underestimated Harvey's abilities. He was quite right, however, about Harvey's writing when he said, " he wrote a very bad hand, which (with use) I could pretty well read ". It could scarcely be worse, and it has been the despair of all who have attempted to transcribe his manuscripts. Dr. Gweneth Whitteridge has seemingly performed the impossible in her triumphant transcription and interpretation of his *De Motu Locali Animalium*. Generations of medical scholars have looked the other way when this terrifying manuscript has come to their notice. Dr. Whitteridge has now, at the instance of this college, given us a new and interesting treatise by the author of *De Motu Cordis*, since, like Aubrey, (with use) she could pretty well read it. In extenuation of Harvey's lack of calligraphic skill it must be pointed out that the work is in the form of rough notes full of abbreviations, additions, and corrections. Perhaps it was a sight of this

manuscript that gave Aubrey his erroneous idea of Harvey's scholarship.

Harvey's Practice

It is recognised that Harvey, from the time of his election to the office of physician to St. Bartholomew's Hospital in 1609, developed a large and lucrative practice in and around London. Aubrey does not enlarge on this, but implies that his practice had been extensive when he says, " His practise was not very great towards his latter end; he declined it unlesse to a speciall friend ". Aubrey also heard him say " that after his Booke of the Circulation of the Blood came out, that he fell mightily in his Practise, and that 'twas beleeved by the vulgar that he was crack-brained; and all the Physitians were against his Opinion and envyed him; many wrote against him ". This distrust of the new science was voiced even by so educated a man as Viscount Conway in his letters to his daughter-in-law, Anne Conway, who in 1651 was under Harvey's care (Nicolson 1930a). This has not uncommonly been the fate of innovators, and is no reflection on Harvey's competence as a doctor. Aubrey does not, however, leave the matter there. He also observes " All the Profession would allow him to be an excellent Anatomist, but I never heard of any that admired his Therapeutique way. I knew several practisers in London that would not have given 3*d.* for one of his Bills; and that a man could hardly tell by one of his Bills what he did aime at ". The last part of this passage may refer merely to Harvey's illegible writing, for his bills, or prescriptions, are indeed hard to decipher, as is well shown in three written for Aubrey himself. In spite of his depreciatory remarks Aubrey thought them worth preserving and they are still among his papers in the British Museum.

But bad handwriting does not necessarily mean that the practitioner is trying to hide incompetence in prescribing, or that he is a bad doctor. Aubrey's statement that he " never heard of any that admired his Therapeutique way " is a serious slur on Harvey's reputation, which is not to be explained solely by the jealousy of other members of his profession engendered by his fame as a scientist.

A pretty tribute was paid to him by a contemporary poet, Abraham Cowley (1663). His *Ode upon Dr. Harvey* celebrates the scientist's control of Nature by his discoveries and in the fourth stanza he sees him as the physician to Medicine itself.

Harvey as Surgeon

There is no hint of his being a bad doctor; but this is a poet's fancy, and it is more apposite to examine Harvey's actual practice as far as it is possible.

He had first presented himself for examination at this college in May, 1603, but was not finally approved and elected to a candidateship until August, 1604, taking the oath on Oct. 5. From this point he steadily progressed. He was elected fellow in 1607, was appointed physician to St. Bartholomew's Hospital in 1609, and became physician extraordinary to King James in 1618. He finally achieved the position of physician in ordinary to King Charles in 1631.

This was not the career of an incompetent doctor. He started without any special advantages, but already in 1605 his father-in-law, Dr. Lancelot Browne, was recommending him for a minor Court post, namely as physician at the Tower of London. Dr. Browne wrote to Lord Salisbury in a letter, recently discovered among the muniments at Hatfield, that he did " never in his life know any man anything near his years [he was only 27] that was in any way matched with him in all points of good learning, but especially in his profession of physician " (Keynes 1958). This sounds like a genuine opinion rather than mere nepotism, and it is to be noted that Harvey's advancement took place for the most part long before his reputation as a scientist was established. This reputation did, indeed, do him more harm than good, as Aubrey testified. His advancement must, therefore, have been due chiefly to his skill as a doctor—and I say doctor rather than physician because he worked as a " general practitioner ", as it would now be called. In the 17th century even a fellow of the College of Physicians carried out surgical operations, though it is difficult to know exactly what Harvey would have done in this line. The Company of Barber-Surgeons had a prior right to the performance of major operations and were called in to " view the patients ", as a consultation was called, when any patient was severely ill with a surgical disease in London. Sir D'Arcy Power (1897c) discovered in the records of the Barber-Surgeons Company an instance in which Harvey was convicted of " ill practice " in this respect. Specially difficult operations, such as " cutting for the stone ", that is removing a stone in the bladder by the perineal route, were done by specialists, and Harvey would not have attempted these. Incidentally, there was a story abroad in 1651 that Harvey had operated on himself for a stone. This was mentioned by Anne, Viscountess Conway, in a letter to her brother John Finch, who was rightly sceptical.

" I was on Saturday ", he wrote, " with Sir Kenelm Digby where I had some philosophical discourse; and he had heard of your marriage, but wondered with me at your story of Dr. Harvey. I must confess I have scarce faith enough to believe he would cut himself but rather believe he voyded that stone you speake of rather than cutt it out; for I do not see it was possible for him in two days to goe abroad otherwise " (Nicolson 1930b).

Harvey would have smiled sardonically at this story. He was much interested in the formation of calculi and wrote in 1638 to Johan Van Beverwijck, a Dutch doctor, a letter recently discovered in which he discussed the subject.

" I knew a noble lady afflicted with calculus," he said, " who used to make little balls with her own hands out of mucilaginous matter, which was a sediment in her urine; she taught and shewed that when these were kept by themselves in a small box they formed calculi spontaneously " (Beverwijck 1641).

Though he did not cut even himself for the stone he must have performed many other operations, and he refers in *De Motu Cordis* to having amputated limbs and excised tumours. He mentions also having occasionally " cured enormous sarcocoeles by the simple means of dividing or tying the little artery that supplied them, and so preventing all access of nourishment or spirit to the part affected, by which it came to pass that the tumour on the verge of mortification was afterwards easily to be extirpated with the knife or searing iron ". Aubrey confirms this when he mentions that Harvey late in life treated by special request " Lady Howland, who had a cancer in her Breast, which he did cutt off and seared, but at last she died of it ". Harvey also mentions having dealt in the same way with an " enormous hernia carnosa " (evidently a sarcoma of the testicle), larger than a human head (Power 1897d). He certainly performed also many gynæcological operations, as can be seen from numerous references in the obstetrical part of *De Generatione.*

It is well known that Harvey included in his will a clause by which he bequeathed to Sir Charles Scarburgh " all my little silver instruments of surgery ". It would be illuminating to have a list of these instruments, but there are no details and I do not know of any similar collection of 17th century instruments having survived. I have looked through the collection of surgical and obstetrical instruments given to the college by Dr. Thomas Prujean on his admission as a candidate in 1653, but they are all large, rather clumsy, steel tools, and clearly quite different from Harvey's bequest, which I figure as having been silver sounds, probes, catheters and dilators, silver-mounted lancets, and other instruments for diagnosis and minor surgery only.

Harvey and the Quacks

The annals of the college provide no direct evidence of what Harvey's practice may have been. One of the chief functions of the college as recorded in the annals was the protection of the monopoly of medical practice in London possessed by the fellows. Some of their prosecutions seem very petty. Thus on July 12, 1605, Walter Priest appeared at the college " on a charge of practising Medicine. He confessed that he had given a purgative potion to a certain man on the advice of Dr. Brown [probably Harvey's father-in-law], but he had done nothing on his own responsibility ". On this occasion the charge was dismissed, but no doubt even so trivial an offence was regarded as being the thin end of the wedge, the thick end including many charges of blatant quackery and even magic.

Thus on Sept. 8, 1615, " Mrs. Bryers, an aged quack with a long face, confessed to the charge namely that she had given to many people sudorifics to cure the French pox, ointments, plaster, potions, extreme unction, both on her own authority and that of other surgeons ". On June 11, 1623, it was charged against Robert Booker that he had given physic to one John Parker lying in St. Martin's Lane. " He anointed him with certaine oiles from the neck to the foote, using at the time of anointing this charme: *Three biters have bitt him, hart, tongue and eye. Three better shall help him presently, God the Father, God the Sonne, and God the holy spirit;* and that also the next day he gave him a drinke which he then dranke, and more he did not to the sick patient, making him believe that he was bewitched and that he would discover who had bewitched him."

Harvey was concerned in the examination of many such charges at the college, but it is impossible not to wonder whether he did not also cock a quizzical eye at some of the methods practised by his colleagues in the college.

In 1665 Marchamont Needham, journalist and dabbler in medicine, published a book called *Medela Medicinae, A Plea For the Free Profession and a Renovation of the Art of Physick*, in which he referred to one " who is (I may well say) the Ornament of our Nation next to immortal Harvey, by name Dr. Willis, Professor of Natural Philosophy in the University of Oxon; one that hath made himself a Physician indeed and Philosopher by Fire and given a good account why he departs from the Doctrine of the Antients touching *Fevers* as well as other things ".

Willis was indeed an eminent physician of great learning and experience, but what are we to think of 17th-century practice when, reading at random in the great doctor's work, we come on the case history of " a Gentile Young Man, being indued with a sharp Blood, and obnoxious to a frequent bleeding at Nose, [who] fell sick of the Small Pox; his Blood of its own accord grew immoderately hot, that the whealks very quickly broke forth all over his Body. Posset Drink, with Marigold Flowers, and other usual things boyled in it, also Juleps, or any Cordials, Tho temperate, and gently provoking sweat, most certainly stirr'd up a Flux of Blood in this person ". In spite of dieting with small beer and " apples roasted tender and dressed with suggar and rose water ", the patient " fell into a most plentiful Bleeding ". Then " Remedies, very many, were tried in vain for the staying of the Blood, at length a little Bag being hung about his Neck (in which was a Toad dryed in the Sun and bruised) he first and immediately perceived ease ". The bleeding stopped and did not recur " whilst he constantly wore this peculiar Medicine in his Bosom " (Willis 1681).

Is it possible to believe that Harvey would have employed a dried toad hung in a little bag about his patient's neck to cure a hæmorrhagic state? As Sir Charles Dodds (1958) has recently pointed out, in Harvey's time the Galenical conception of disease and the pharmacopœias were accepted without question. In fact, Sir Charles states, " apart from opium preparations, purgatives, and emetics, the rest of the pharmacopœia could be dismissed ". None of these remedies " had any pharmacological or therapeutic activity ". Sir Charles poses the paradox of Harvey, the scientist, practising by totally unscientific methods, and apparently content to do so without criticism or question. He explains it by the belief that Harvey did not associate his discoveries in science with the practice of medicine and therapeutics. They were unrelated in his mind to treatment.

Aubrey's Anecdotes

Let us now return to John Aubrey and his belittlement of Harvey as a doctor. Aubrey himself was greatly interested in medicine and his writings contain many anecdotes related to various diseases and their cure, and of strange happenings. Thus he relates that

" A Fellow in North-Wales, shrowding of a Tree fell downe on his head, and his Braine being turned, lay for dead. A Mason being thereby, advised that he should have a good strong coffin made, and his feete to come to the end of it, and his head not to touch the other end by two inches. He layeth the Man in the Coffin on a Table-board, and then with a huge Axe, gave a sound Knock at the feet, to turne by that contrary motion his braine right againe. After the blow was given the fellow gave a groane and spake: and he recovered." Again he tells of how " Mr. Bonham's wife had two Children at one birth, the first time; and he being troubled at it, travelled: and was absent seven yeares. After his return he got his wife with Child, and she was delivered of seven Children at one Birth."

Then Aubrey adds: " Dr. Wm. Harvey told me that one Mr. Palmer's Wife in Kent did beare a Child every day for five daies together." This Aubrey capped with the story of:

" Mris Hine the Vicar's wife of Kington St. Michael, a very able midwife, who told of a lady who was brought to bed at Dorchester, was delivered first of a Sonne (now living and the Heir) and afterwards for eight days together, every day another Child: some whereof had heads and Armes and no lower parts; other had lower, but no upper parts."

Aubrey followed this with an anecdote of " two Children born in the grave ". Harvey then countered with the story of a

" certain Knight in Kent, who having gott his Wive's Mayd with Child, sent her to London to lie-in under pretence of seeing her friends. She was brought to bed then about Michaelmas; and after some convenient time she returned to her Lady. She found herself not well, and in December following she fell in labour again, and was delivered of another child."

Harvey was not responsible for the next story.

A woman who half an hour after bearing a normal child " was delivered of a Monstrous-birth, haveing two Heades the

one opposite to the other. About four O'Clock in the after Noon the same day it was christened Martha and Mary, having two pretty faces, and lived till Fryday next".

But Aubrey characteristically draws me into irrelevancies. It is more to my point that he records a remedy

"To cure the Thrush, Take a living Frog, and hold it in a Cloth that it does not go down into the Child's Mouth; and putt the Head into the Child's Mouth till it is dead, and then take another Frog." Again "To Cure the Tooth-ache. Take a new Nail, and make the Gum bleed with it, and then drive it into an Oak. This did Cure William Neal, Sir William Neal's Son, a very stout Gentleman, when he was almost Mad with the Pain and had a mind to have Pistoll'd himself."

It is plain that Aubrey preferred to believe that to effect the cure the nail must be driven into an oak rather than to attribute it to having opened an abscess by pricking the gum. Aubrey was, in fact, an inveterate believer in magic and liked the practice of physic to border on the supernatural. He knew nothing of the power of suggestion and was no more critical of current misinterpretations of cause and effect than the eminent Dr. Willis. Harvey, I suggest, though practising Galenical medicine, was not to be deceived by the absurdities that contented so many of his contemporaries. His mind was of a different cast and instinctively he evinced a *Scepsis Scientifica* in practice, but having no alternative remained faithful to the conventional pharmacopœia of his time, as Sir Charles Dodds has determined by examining the prescriptions approved by him at St. Bartholomew's Hospital. It was this sceptical attitude which made Aubrey think him a bad doctor, and no doubt he found others to agree with him. It is really a tribute to Harvey's honesty in the face of therapeutic poverty due to no fault of his own.

Harvey's Patients

Looking at Harvey's practice from another angle, it is difficult to imagine that, if he was the bad doctor that Aubrey suggests, he would have kept the confidence of the kind of person that he habitually attended. He was wise enough not to attend his own family, for we know that, when his brother Eliab Harvey was ill in 1643, it was Dr. Baldwin Hamey who was called in to treat him (Keevil 1953). I would that we knew more of Harvey's actual patients by name. We do know that he was trusted by two Kings of England, and of a certainty by many members of their courts. In fact we have the report sent to the King when Harvey had been sent down to Milton during the siege of Plymouth to attend on Prince Maurice, who was suffering from "a slow fever". The report is dated Oct. 17, 1643, and is now in the British Museum among Prince Rupert's correspondence, Harvey was friend and doctor to Sir Francis Bacon, who (although Harvey spoke of him to Aubrey with some scorn) did indeed possess one of the shrewdest intellects of his time. He was the close friend and physician (as Aubrey notes) of Thomas, Earl of Arundel, and accompanied him as doctor to the party when the Earl was sent as Ambassador Extraordinary to the Emperor Ferdinand in 1636. Harvey was for many years physician to Viscount Conway and his family, in particular to Anne, the Viscount's daughter-in-law. Anne Conway, one of the most distinguished ladies of her period, suffered from an inveterate headache, for which Harvey treated her for a long time without success (Nicolson 1930c). She was also attended by Sir Theodore de Mayerne, Dr. Thomas Willis, and others. Willis related that ultimately Harvey persuaded her to go to Paris to have her skull opened by the trepanning iron, but even the French surgeons dared not take the risk (Willis 1683).

John Selden, the celebrated jurist, and an almost exact contemporary of Harvey, was evidently his friend and patient. In his *Table Talk* Selden (1696) related that

"A Person of Quality came to my Chamber in the Temple, and told me had two Devils in his Head, and just at that time one of them bid him kill me.' Selden took him in hand, and perceiving that it was only melancholy that troubled him, gave him a card "lap'd up handsome in a piece of Taffata" with instructions to hang it about his neck, to eat but little supper, to say his prayers duly when he went to Bed, and "made no question but he would be well in three or four days". Next time they met "he said he was much better, but not perfectly well", or perhaps he had not dealt plainly with Selden, for now, he said, he had four devils in his head. Two were gone with the first treatment, but the other two still troubled him. The treatment was repeated and the patient returned three days later to report himself quite well. Selden, fearing he might relapse, then "told him that there was none but himself and one Physician more in the whole Town that could cure the Devils in the Head and that was Dr. Harvey (whom he had prepared) and wished him, if ever he found himself ill in his absence, to go to him".

This relation throws light on Harvey in the role of psychiatrist, though the gentleman remained well and did not have to trouble him in that capacity. This is only one of several examples of Harvey's knowledge of neurology and psychiatry gathered by Dr. Richard Hunter and Dr. Ida Macalpine. Attention may also be drawn to the fact that Harvey was consulted by the famous Robert Boyle about his weak eyes; on this occasion Harvey told him that he once had a patient "that had a confirmed Cataract in his Eye and yet upon the use of Physick, to which he could not ascribe so wonderful an effect, that Cataract was perfectly dissipated and the Eye restored to its wonted function" (Boyle 1663). Harvey was not deceived into attributing unlikely effects to the drugs that he employed.

Gideon Harvey

It would not be honest if I were to give the impression that nearly every contemporary reference to Harvey redounded to his credit. I must therefore mention that at least one younger physician criticised him for clinical incompetence. This was his namesake, Gideon Harvey, a copious but unimportant writer on medical subjects.

Gideon Harvey was born about 1640 and qualified as a doctor of medicine at a French university at an early age; but he was too young to have come into professional contact with William Harvey and is unlikely to have known him at all. His strictures must therefore have been based on hearsay, though they do not read like inventions. His best known book is *The Art of Curing Diseases by Expectation*, published in 1689. This is a scurrilous work, but at least Gideon Harvey shows a wholesome scepticism as to the efficacy of the conventional drugs and an appreciation of the current fallacies in association of cause and effect. The Art of Expectation consisted, however, in doing nothing, and Gideon Harvey derides this also. "These Expectation Doctors", he truly says, "are the Safe men, the good Children's Doctors, much in request among some wise Women. They are such, as in difficult Diseases kill by omission, and cure easie Distempers by seeming to do something of no importance". The greater part of the book is an amusing diatribe against the medical profession in general and the College of Physicians in particular. Naturally William Harvey does not escape, Gideon calling him "the greatest Anatomist of his time and no extraordinary physician" (Harvey 1689a). He then relates that Harvey's "erroneous Judgment was very remarkable in the prescription of a purge for Esq. Rainton of Enfield, where the Apothecary refraining to

prepare more than half the proportion, notwithstanding gave him fourscore stools, which otherwise according to the Doctor's measures must unavoidably have scower'd him from the close Stool into the other world ". I think we may assume that the mistake was made by the apothecary, not by Harvey.

Another patient was Mr. Farwel, Barrister of the Temple, complaining of abdominal trouble with many symptoms. He was attended by William Harvey with several other doctors, including Dr. Prujean, but, says Gideon, " Dr. Harvey ingrossed to himself the speaking part by reason of his extraordinary claim to Anatomy ". After a " long contrectation of all the abdomen, he did very magisterially and positively assert all his Symptoms to arise from an Aneurism of an Artery and therefore incurable ". The patient then went to Sir Theodore de Mayerne, who after a brief examination undertook to cure him. Luckily for him the tumour proved to be solid and due to enlarged mesenteric glands, which presently resolved. Harvey had been deceived, just as so many others of us have been since his time, by transmitted pulsation, or, as Gideon calls it, " a Vibration ".

A third patient of William Harvey was a tailor of Fleet Street, complaining of sciatica. Harvey (says Gideon) engaged to cure him if he would " sequester himself from his Trade for three Months ", would pay fifty pounds, and would submit to having his leg " laid open to the bone by cutting or burning ". The patient objected to the third condition, and went off to another physician " of much lower form, who advised him to the Bath, where he received a perfect cure in six weeks ". Evidently the cure of slipped disc by the Art of Expectation is not so modern as we have thought. On this occasion Gideon Harvey observes that " no doubt but Dr. Harvey in Anatomy and happiness of theoretic discoveries might justly pretend the precedency of all his Contemporaries, and others before and since have also arrived to a great proficiency in Cat and Dog cutting, also Calf-head and Sheeps-pluck dissecting; yet few of 'em when concerned in Practice were gifted with sagacity to know Diseases when offer'd to their view, much less of curing them; in which curative particular the Thinking Physician has the advantage, though the Prating Physician by his pretended Anatomy ingrosses the opinion of Mankind " (Harvey 1689b).

Thus the jealousy of lesser men can be seen pursuing William Harvey beyond the grave and voicing the common opinion of which Aubrey had taken note. It does not lead me to believe that Aubrey was right in thinking him a bad doctor, but it serves to show how he was sometimes misled by listening too much to gossip at his drinking parties.

The Battle of Edgehill

Retailing gossip as if it were to be trusted has been a common charge against Aubrey by his critics. More serious is an accusation of deliberate fabrication about Harvey (Stewart 1946). The occasion of this was Aubrey's statement about the battle of Edgehill, fought on October 23, 1642.

" When Charles I by reason of the Tumults left London, he [Harvey] attended him, and was at the fight of Edge-hill with him; and during the fight, the Prince and the Duke of Yorke were committed to his care. He told me that he withdrew with them under a hedge, and tooke out of his pockett a booke and read; but he had not read very long before a Bullet of a great Gun grazed on the ground neare him, which made him move his station ".

It is to be noted that Aubrey relates this as taken from Harvey's own mouth—"He told me "—and Aubrey could have had no possible motive for inventing such a story. Yet Dr. Stewart thinks that evidence from other sources " completely demolishes " Aubrey's story, which, he says, " has not a shred of evidence to support it ". I have examined the sources for myself and find that an anonymous writer, partially quoted by Dr. Stewart against Aubrey, after stating that the Prince and the Duke of York were at the battlefield of Edgehill by 8 o'clock in the morning with the King, further relates that

" It was at least two of the clock in the afternoon before the armies came together in the field where the rebels had kept themselves in order without motion from the morning and had gotten the advantage of the hill, and saluted us with 2 or 3 canon-shot before our ordnance came and were planted. The shot from the canon on either side did not much hurt in the beginning, though where his Majesty and his Children were, many shots fell very near his Royal Person " (Carte 1739).

This seems to agree perfectly with Aubrey's story, since there is no difficulty in believing that at this stage Harvey was with the King and in charge of the two boys. No wonder that he read a book during the hours of waiting from 8 in the morning till after 2 o'clock. All the evidence brought forward by Dr. Stewart as related by the Duke of York and by Dr. (later Sir John) Hinton concerns events which took place later in the afternoon after the initial routing of the left wing of the rebels by the Royal cavalry. Harvey was a non-combatant and is not likely to have stayed with the King, who, as the battle developed, was with the foot-soldiers and tried to get his sons out of harm's way, though they were eager to take part. There is no ground for stating that these accounts " completely contradict Aubrey's romantic little story ". Aubrey's story is sober and factual, not romantic. The romance was added by the embroideries of Harvey's biographers.

Further, Aubrey follows his story with Harvey's telling him

" that Sir Adrian Scrope was dangerously wounded there and left for dead amongst the dead men, stript; which happened to be the saving of his life. It was cold, clear weather, and a frost that night, which staunched his bleeding, and about midnight, at some houres after his hurte, he awaked, and was faine to drawe a dead body upon him for warmethsake ".

This is fully corroborated by Dr. Stewart's second witness, except that he is less accurate than Aubrey in calling Scrope " Sir Gervase " (Clarke 1816).

My conviction that Aubrey was telling the truth has been further strengthened by the realisation that the Scottish National Portrait Gallery in Edinburgh possesses a picture by Dobson of the Prince of Wales in armour with another boy resembling the Duke of York. In the left-hand lower corner, above a decapitated head, is a battle scene with a cavalry skirmish, indicating clearly that the picture was intended to commemorate an incident of the Civil War. This picture was given to Harvey by the King, and passed at his death to his brother, Eliab. It remained in the possession of the family until it was sold to the Edinburgh gallery in 1946.

I cannot now examine Aubrey's other statements in detail. His description of Harvey's eccentricities in old age is corroborated by the further account given by Harvey's niece, and his description of the last hours bears the stamp of truth. I ask you, therefore, to believe that Aubrey's picture of Harvey is in the main accurate—though his natural inclinations led him sometimes into a misinterpretation of Harvey's qualities. Aubrey's was not a wholly admirable character, but he was not a liar and he has bequeathed to us the most life-like portrait of Harvey that we possess.

I am indebted to the Registrar for permission to read the English translation of the Annals of the College, and Mr. L. M. Payne, assistant librarian, for help and advice.

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LIPÆMIA AND BLOOD COAGULATION WITH SPECIAL REFERENCE TO THE STYPVEN TECHNIQUE

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THE original observation by Fullerton et al. (1953) that there was a shortening of the 'Stypven'-time (i.e., the plasma clotting-time accelerated by Russell-viper venom) after the ingestion of fat created considerable interest, and this technique has been applied to fat-feeding experiments which have been reported by Hall (1956), O'Brien (1956), Maclagan and Billimoria (1956), and Mersky and Nossel (1957). Because stypven is fat-free, it is a particularly convenient thromboplastin for this purpose, and it gives reproducible clotting-times on the same plasma specimen. A number of modifications of the method are in use, some of which do not regularly demonstrate the effects of fatty meals or of added fat. Irregularities in our results with such methods, and a lack of other reliable techniques, indicated the need for a thorough study of this popular method. The potential importance of these techniques in relation to the problem of atheroma, which was the basis of the earlier work, receives some support from a recent study (McDonald and Edgill 1957) in which a small but statistically significant shortening of the stypven-time was shown in patients with recent occlusion of a coronary artery.

In previous stypven methods an indefinite delay (Fullerton et al. 1953) or a defined time lag of 1 minute (Poole and Robinson 1956, O'Brien 1956) has been allowed to lapse between the addition of venom and calcium chloride. We found this delay to be undesirable and proposed an "instantaneous" technique in which venom and calcium are added simultaneously (Billimoria, Lockey, and Maclagan 1957). This appears to be a superior method for demonstrating the effects of added fats. O'Brien (1958) has also studied the effects of varying the order of the addition of reagents in this system, and has given evidence for the existence of a time-consuming reaction between stypven and factor 5. This paper reports further results with the instantaneous technique, and an investigation of the influence of lipæmia on the reaction.

Materials

All reagents were adjusted to the physiological ionic strength of 0·15 by adding appropriate amounts of sodium chloride.

Calcium chloride stock solution.—Commercial calcium chloride when made up in water has a pH between 9 and 11, and it contains calcium hydroxide, so that after exposure to air some carbonate is formed which gradually sediments. Hence the reagent was prepared as follows. Calcium carbonate, analytical reagent (A.R.), (approximately 100 g.) was gradually added with stirring to A.R. hydrochloric acid of approximately 5*N* until a slight excess of carbonate remained undissolved. The solution was filtered, and calcium was estimated by titrating an aliquot. The solution was then diluted with water to obtain a clear stock *M*-solution which may be stored indefinitely and diluted as required for the other reagents.

Stypven (Burroughs Wellcome).—1 ampoule (0·5 mg.) was dissolved in 5 ml. water, and was found to be 0·1 *M* with respect to sodium chloride, for which allowance is made below. The solvent supplied by the makers of stypven contains 0·5% w/v of phenol. Since phenol itself was found to accelerate clotting, its use has been avoided.

Venom-calcium chloride.—1 ampoule of stypven was dissolved in 5 ml. of 0·1 *M* sodium chloride, and 5 ml. of *M*/30 calcium chloride was added.

Venom-saline.—1 ampoule of stypven was dissolved in a solution of 5 ml. of 0·05 *M* sodium chloride.

Calcium-saline.—*M*/15 calcium chloride was diluted with an equal volume of 0·1 *M* sodium chloride solution.

Physiological saline.—0·9 g. of sodium chloride was dissolved in 100 ml. of distilled water.

Methods

Blood was collected in a siliconed syringe with a siliconed needle and added to $^1/_9$ volume of cold sodium citrate solution (3·8% w/v). The mixture was immediately cooled by immersing the tube in ice-cold water and centrifuged at 4000 r.p.m. (relative centrifugal force 3500 *g*) for 10 minutes at 0–4°C. Plasma was removed with a siliconed pasteur pipette, and stored in a siliconed tube at 0°C. Clotting tests were performed within 1 hour of centrifugation, although little change was observed for up to 3 hours. Soda-glass tubes 3 × $^3/_8$ in. with 'Parafilm' cover-slips were used for the clotting tests. The appropriate reagents were warmed to 37°C just before use.

"*Instantaneous*" *technique.*—0·1 ml. of psysiological saline and 0·1 ml. of plasma was warmed to 37°C for 1 or 2 minutes. 0·2 ml. of venom-calcium chloride was then added, and the clotting-time was recorded. The influence of lipids on the system was studied by substituting 0·1 ml. of lipid suspension for saline. The lipids were suspended in saline with the aid of a mechanised vibrator working at 60 cycles/sec. (supplied by H. Mickel of Gomshall, Surrey).

"*Delayed*" *technique.*—0·1 ml. of physiological saline and 0·1 ml. of plasma was warmed to 37°C for 2 minutes. 0·1 ml. of venom-saline was then added, and the mixture was incubated for 1 minute at 37°C. 0·1 ml. of calcium-saline was then added, and the clotting-time was recorded.

Lipæmia.—The degree of visible lipæmia was usually measured on a nephelometer (Evans Electroselenium, Ltd.). The $^3/_8$ in. ground 'Perspex' rod was set at 100 turbidity units, which was approximately equal to 125 thymol-turbidity units (Maclagan 1947). All plasma-turbidity measurements were

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made in 3 × 3/8 in. glass tubes. In some experiments the optical density ($E \frac{1\text{ cm.}}{625\ m\mu}$) was measured instead.

Unesterified fatty acids (U.F.A.).—Estimations were carried out by the method of Dole (1956) on 1 ml. quantities of plasma.

U.F.A. liberated by stypven.—1 ml. of plasma and 1 ml. of venom-saline was warmed to 37°C for varying times, and 5 ml. of solvent mixture (40 vol. isopropyl alcohol, 10 vol. *n*-heptane, and 1 vol. *N*-sulphuric acid) was added. The mixture was vigorously shaken and placed on ice. The top solvent layer (3 ml.) was titrated as above.

Lysophosphatides.—These were prepared from egg-yolks by a slight modification of the method of Levene and Rolf (1923). Stypven was used instead of cobra-venom and cadmium chloride was omitted during purification. The crude lysophosphatides as precipitated from the reaction mixture with acetone were subjected to continuous extraction with acetone for 12 hours. The acetone extract was rejected and the solids thoroughly extracted with ethanol containing about 20% by volume of water. The latter extract was evaporated to dryness and thoroughly extracted with ether. The ether-insoluble lysophosphatides were used in the clotting experiments without further purification.

Paper chromatography.—1 ml. of control plasma, and 1 ml. of plasma treated with 1 ml. of venom at 37°C for 15 minutes, were separately extracted with ethanol-ether (3/1 by volume); the extracts were filtered and evaporated to a small volume, and aliquots were spotted on silicic acid treated paper. The chromatogram was run and developed by the method of Lea et al. (1955). Lyso-lecithin (R_F 0·27) formed in the reaction with venom was easily differentiated from the unchanged lecithin (R_F 0·63).

Results

Minor technical variations influencing the system are concerned with the concentrations of calcium chloride and stypven, and with adjustment of the ionic strength of the clotting mixture.

Fig. 1 shows that with the quantities of reagents used the optimum calcium chloride concentration required is in the neighbourhood of *M*/30 both with fasting and with lipæmic plasma. While other strengths of calcium chloride make the system more sensitive to the effects of lipæmia, such a system cannot easily be reproduced since minor pipetting errors have too great an influence on the results. In particular *M*/10 calcium chloride, suggested by Fullerton et al. (1953) and by the makers of stypven, suffers from this disadvantage. Similar results to those given in fig. 1 were obtained when fasting plasma specimens compared with plasma made artificially lipæmic by the addition of a suspension of butter.

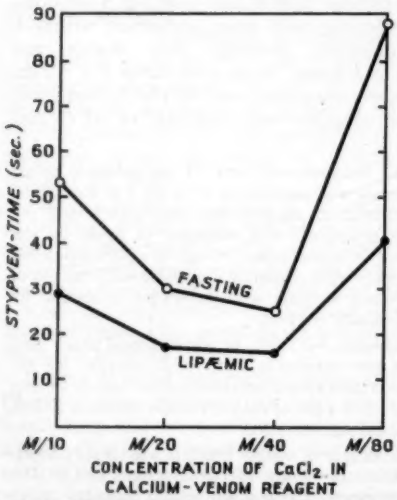

Fig. 1—Effect of calcium chloride concentration on stypven-time in fasting and lipæmic plasma specimens at constant ionic strength (0·2).

A similar experiment showed that the optimum amount of stypven was approximately that suggested by the makers, and that small variations from this figure were relatively unimportant. The stypven solvent as supplied contains 0·5% of phenol; this was not used because we found that phenol itself has an accelerating effect on the clotting-time.

TABLE I—EFFECT OF VARIATIONS IN SALT CONCENTRATION ON STYPVEN CLOTTING-TIMES

Saline concentration (g. per 100 ml. NaCl)	Final ionic strength	Clotting-time (sec.)		% difference
		Plasma alone	Plasma + butter	
0	0·088	19·7	13·0	34
0·85	0.125	24·3	13·6	44
1·70	0·163	33·7	13·1	61
3·40	0·238	79·5	30·0	62

0·1 ml. plasma + 0·1 ml. saline + 0·1 ml. water ± 0·1 mg. butter + 0·1 ml. venom-$CaCl_2$ mixture.

Table I shows that variations of ionic strength of the medium influence the clotting-time, and that the use of low ionic strengths diminishes the effects of added fat. As a result of this experiment the physiological ionic strength of 0·15 was chosen for general use.

Instantaneous and Delayed Techniques

The original delayed techniques consist in incubating the plasma with venom for an unspecified period or for 1 minute before the addition of calcium chloride. As previously reported (Billimoria et al 1957) this delay diminishes the influence of certain added fats. Table II shows that this masking action of delay also applies to the results of fatty meals, since in each of the three subjects the drop in stypven time due to fat was greater with the instantaneous than with the delayed technique.

TABLE II—EFFECT OF FAT FEEDING ON STYPVEN-TIME IN THREE SUBJECTS USING THE INSTANTANEOUS AND DELAYED TECHNIQUES

Subject no.	Method	Stypven-time (sec.)		Difference (sec.)
		Fasting	3 hr. after 2 oz. butter	
1	Instantaneous ..	38	17	21
	Delayed	32	28·5	3·5
2	Instantaneous ..	37	21	16
	Delayed	34	23·5	10·5
3	Instantaneous ..	54·5	32	22·5
	Delayed	42·5	30·5	12

We have found that venom has a lipolytic action on plasma and that within a minute's incubation substantial quantities of fatty acids are liberated which may influence coagulation. Further, more fatty acids are liberated from lipæmic than from fasting plasma as estimated by microtitration. Data on this lipolysis during incubation is presented in table III. The two typical examples show that as the time of incubation of plasma with venom was increased from 0 to 1 minute, increasing amounts of fatty acids were liberated, and at each of these times more fatty acids were obtained from lipæmic than from fasting plasma.

Further data on fat feeding were obtained by experiments on two volunteers who ate fat-free and fatty breakfasts on consecutive days, blood specimens being collected at 2 hours and 4 hours after each meal. Clotting was observed with the delayed and instantaneous methods and U.F.A. determinations were carried out on the plasma specimens before and after incubation with venom for 1 minute. Nephelometric readings were taken on the plasma specimens to determine the degree of lipæmia. Table IV shows again that more fatty acids were liberated

TABLE III—LIPOLYTIC ACTION OF STYPVEN ON FASTING AND LIPÆMIC PLASMA

Plasma sample (1 ml.)	Incubation-time (min.)	U.F.A. (μEq. per litre)		Fatty acids liberated by stypven (μEq./l.)	
		Fasting	Lipæmic	Fasting	Lipæmic
A	0	298	310	0	0
	0·5	510	807	212	497
	1	712	925	414	615
B	0	705	302	0	0
	0·5	705	604	0	302
	1	815	735	110	443

from lipæmic than from fasting plasma after 1 minute's incubation with stypven. In these experiments also the instantaneous method showed more response to fat than the delayed method, and in one case the delayed method showed a rise rather than a fall in clotting-time after the fat feed. Fatty acids liberated by stypven do not seem to have any additive shortening effect on the clotting time, as might have been anticipated from the results of Poole (1955).

Fat-feeding Experiments by the Instantaneous Technique

In view of these results the delayed method was abandoned and further fat-feeding experiments were carried out by the instantaneous technique. Table v gives the results on a single volunteer who took a number of 2 oz. fat feeds over a period of 3 months. The fasting time of this subject was usually 34–36 seconds, and a clear response to fat was obtained on each occasion, the response being about equal with butter and with margarine. On eight out of nine occasions the shortest stypven-time occurred at the peak of lipæmia, whereas no similar correlation was observed between the U.F.A. and stypven-time. Thus in three experiments the U.F.A. values were slightly increased after the fatty meal, and in the other three experiments a decrease was observed. This volunteer did not develop any tolerance to fat as observed with one subject by O'Brien (1957).

Further data on seven volunteers of various ages are shown in table VI; all showed a drop of the stypven-time after meals of butter, margarine, or olive-oil, irrespective of the nature of the fat fed. As little as 14 g. of fat produced a substantial lowering of the stypven clotting-time, and larger amounts produced drops of up to 50%. There was a striking correlation between the drop in stypven-time and the degree of lipæmia, as shown in fig. 2. Maximal lipæmia was usually seen 3 hours after the meal, but some younger subjects showed a maximum at $1^1/_2$ hours.

The instantaneous stypven system is very sensitive to the in-vitro addition of certain fats, and fig. 3 shows that butter depressed the stypven-time far more than did margarine at the same concentration. Thus the addition of 10 mg. of butter depressed the stypven-time from 36 to 6·6 seconds, whereas the same amount of margarine gave a clotting-time of 28 seconds. 0·1 mg. of margarine had practically no effect, whilst the same amount of butter produced over 50% depression of the stypven-time. These results are similar to those previously reported (Maclagan and Billimoria 1956).

Lysophosphatides and Coagulation

The lack of correlation between U.F.A. values and stypven-times suggested that some other aspect of the lipolytic action of the venom must be important in relation to coagulation. One possibility was that the liberation of fatty acids was associated with the production of lysophosphatides which might influence clotting.

TABLE V—EFFECT OF FAT FEEDING ON STYPVEN-TIME IN A NORMAL MALE SUBJECT AGED 21

Fat	Time after meal (hr.)	Optical density	U.F.A. (μEq. per litre)	Stypven clotting-time (sec.)	Drop in stypven-time after fat
Butter	0	213	..	36	..
	3	255	..	31	+ 5
	6	388	..	23·5	+12·5
Butter	0	66	..	37	..
	3	218	..	26·5	+10·5
	6	203	..	31	+ 6
Butter	0	258	..	36	..
	3	808	..	26	+10
	6	221	..	25	+11
Butter	0	194	197	34	..
	3	365	381	27	+ 7
	6	242	244	36	− 2
Butter	0	180	474	34·5	..
	3	253	309	30	+ 4·5
	6	500	309	20	+14·5
Margarine	0	97	418	35	..
	3	222	276	26·5	+ 8·5
	6	320	402	22·5	+12·5
Margarine	0	219	236	34	..
	3	360	200	22	+12
	6	490	383	19	+15
Margarine	0	240	237	34·5	..
	3	325	136	28·5	+ 6
	6	214	213	35	− 0·5
Butter	0	260	151	40·5	..
	3	550	216	35	+ 5·5
	6	890	288	24·5	+16

Meals consisted of toast, jam, and 2 oz. of butter or margarine. Tests were at weekly intervals and are arranged in chronological order.

Evidence for this hypothesis was obtained by introducing a lysophosphatide mixture, prepared by the action of stypven on egg-phosphatides as described above, into the stypven system. Table VII shows that the lysophosphatides affected coagulation significantly, and they had definite anticoagulant properties in the system studied in amounts as low as 0·0125 mg. per system. Furthermore the effect was greater with lipæmic than with fasting plasma.

The production of lysophosphatides in plasma was studied in two ways. Firstly, when plasma and stypven

TABLE IV—STYPVEN-TIMES AND U.F.A. ESTIMATIONS AFTER TEST-MEALS IN TWO NORMAL SUBJECTS

Time after meal	Stypven-time (sec.)		Drop in stypven-time (sec.)		U.F.A. (μEq. per litre)		Rise in U.F.A. due to stypven	Nephelometer reading (arbitrary units)
	Instantaneous	Delayed	Instantaneous	Delayed	Before stypven	After stypven		
Subject A:								
2 hr.—fat-free	30·5	32·5	+11·5	+2·5	130	340	210	20
2 hr.—fatty	19	30			144	720	576	120
4 hr.—fat-free	28·5	33·5	+11·5	+8·5	390	680	290	18
4 hr.—fatty	17	25			158	731	573	80
Subject B:								
2 hr.—fat-free	28·5	31·5	+8	+0·5	118	524	406	24
2 hr.—fatty	20·5	31			332	906	574	160
4 hr.—fat-free	27	31	+3·5	−4	392	755	363	22
4 hr.—fatty	23·5	35			210	730	520	94

Meals consisted of toast and jam, with or without $1^1/_2$ oz. of butter.

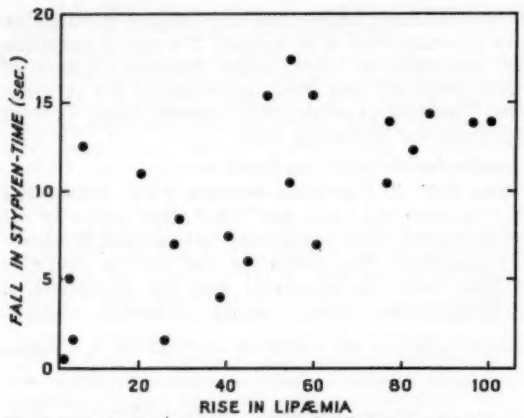

Fig. 2—Relation between drop in instantaneous stypven-time and rise in lipæmia after a fatty meal. Nephelometric readings, in arbitrary units, were taken as a measure of lipæmia (correlation coefficient +0·65, P<0·001).

mixtures were incubated for 15 minutes, the presence of lysophosphatides was readily established by paper chromatography as described above. Secondly, experiments in vitro showed that the lipolytic action of venom on plasma was confined to the phospholipids and that the neutral fat was not affected. Thus, when plasma-lipids were separated into acetone-soluble and acetone-insoluble lipids and each fraction was treated in saline suspension with venom at 37°C, fatty acids were liberated only from the phospholipid (acetone-insoluble) fraction.

TABLE VI—EFFECT OF 13 FATTY MEALS ON STYPVEN-TIME IN SEVEN NORMAL SUBJECTS

Age (yr.)	Sex	Fat (g.)	Time after meal (hr.)	Nephelometer reading	Stypven clotting-time (sec.)	Drop in stypven-time (sec.)
21	F	B—42	0	13	36·5	..
			1½	90	22·5	+14
			3	62	20	+16·5
22	M	B—42	0	17	31	..
			3	62	24·5	+ 6·5
			6	22	32	− 1
22	M	B—42	0	20	39	..
			3	22	34	+ 5
			6	25	26·5	+12·5
23	M	B—42	0	24	38·5	..
			2	53	30	+ 8·5
			3	52	32	+ 6·5
23	M	B—42	0	22	29	..
			1½	108	18	+11
			3	170	15	+14
53	M	B—14	0	24	28·5	..
			3	106	19	+ 9·5
53	M	B—28	0	22	32·5	..
			3	118	19	+13·5
53	M	B—42	0	28	34·5	..
			1	88	28	+ 6·5
			3	82	24	+10·5
			6	82	16	+18·5
53	M	B—42	0	22	33·5	..
			½	24	24·5	+ 9
			1	32	23·5	+10
			2	75	24	+ 9·5
36	M	O—28	0	14	40·5	..
			3	24	33	+ 7·5
36	M	O—28	0	16	32·5	..
			3	102	19	+13·5
53	M	Mg—14	0	18	32	..
			3	58	25	+ 7
36	M	Mg—42	0	16	45	..
			3	76	23·5	+21·5

B = butter, Mg = margarine, O = olive-oil.

It therefore seems certain that the U.F.A. obtained in the earlier experiments after stypven action must have originated from phosphatides, and that significant amounts of lysophosphatides must be liberated during the delayed stypven method. Thus, assuming a liberation of about 500 μEq. per litre of U.F.A. (an average figure after 1 minute's incubation of lipæmic plasma), the equivalent amount of lysophosphatide is 0·025 μg. per system. Table VII shows that this amount is sufficient to produce a considerable lengthening of clotting-time. In the instantaneous method, however, the amount of lysophosphatide produced during the usual 15–30 seconds of clotting-time would be too small to exert much effect. Similarly the amount of lysophosphatide produced from fasting plasma, even after 1 minute's incubation, is relatively small.

These considerations suggest a probable explanation of the difference between the instantaneous and delayed techniques in their response to fat feeding.

Discussion

The main conclusion from this study is that the lipolytic action of Russell-viper venom exerts an important influence on clotting, and that this influence varies with the concentration of fat in the plasma. Thus, when stypven is added to plasma, lipolysis starts at once, and it has progressed significantly after the usual 1 minute's incubation. Although more lipolysis occurs with lipæmic than with fatty plasma, this lipolysis appears to mask the accelerating effect of fat, since the longer the incubation period allowed the smaller is the influence of lipæmia on the clotting-time. The substrate for the lipolytic enzyme is in the phosphatide fraction of the plasma-lipids, and neutral fats are not affected. The masking effects of lipolysis can therefore be explained by the production of lysophosphatides, which were found to exert an inhibitory effect on coagulation. Lipæmic plasma produced more lysophosphatides than fasting plasma and the resulting inhibition of coagulation would be in opposition to the accelerating effect of lipæmia.

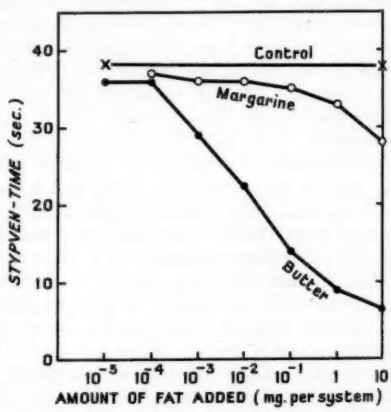

Fig. 3—Effect of adding butter or margarine in vitro on instantaneous stypven system, using fasting normal plasma.

This pronounced inhibitory effect of egg-lysophosphatides on blood coagulation appears to be a new observation. The effect is not confined to the stypven technique since we have also seen it in plasma-recalcification experiments. We have not found any previous reports dealing with this effect, although a number of workers have reported absence of coagulant activity with lysophosphatide preparations (Chargaff and Cohen 1939, Poole and Robinson 1956, Rouser et al. 1958).

TABLE VII—EFFECT OF EGG-LYSOPHOSPHATIDES ON STYPVEN-TIME OF TWO FASTING AND TWO LIPÆMIC PLASMA SPECIMENS

Lysophosphatide (mg. per system)	Stypven-time (sec.)			
	Lipæmic		Fasting	
0	19·5	23	40·5	28.5
1	71	63	58	39
0·2	36	40	50	34
0·1	28	38	47·5	33
0·05	24·5	32	44·5	35
0·025	24·5	28·5	44·5	34.5
0·0125	22	24·5	41·5	31
Nephelometer reading	130	70	14	44

These results suggested a modification of the usual stypven technique (which we have described as the instantaneous method) in which the venom and calcium chloride are added to the plasma simultaneously in an isotonic medium. With this method the results of fat feeding are very striking, even with amounts as small as 14 g., and considerable acceleration of clotting was recorded in every experiment. Experiments in vitro suggest that the addition of neutral fats has no effect on stypven systems (Maclagan and Billimoria 1956, Rouser et al. 1958). Certain phospholipids, on the other hand, are known to be very active, and the post-prandial acceleration is probably due to changes in the plasma-phospholipids accompanying fat absorption, as suggested by O'Brien (1957). Contrary to our previous experience with the delayed method, we now find little difference between the effects of feeding different fats, such as butter, margarine, or olive oil, when the instantaneous technique is used. Since olive oil is almost free from phospholipids, a proportion of those phospholipids present in lipæmic blood presumably has an endogenous origin.

Experiments in vitro with the instantaneous method still show a considerable difference between the effects of adding milk fats, such as butter, and other fats to the clotting system, since the former are much more effective. In view of the similarity of the results of feeding different fats, however, this observation has doubtful physiological significance.

The results as a whole suggest that the instantaneous stypven technique, although open to criticism as being unphysiological, is an improvement on previous methods, and is well adapted to the study of the effects of fatty meals on blood-coagulation. The relation of the test to pathological processes is being explored further.

Summary

When Russell-viper venom ('Stypven') is added to plasma, lipolysis starts immediately and may exert a significant effect on the clotting-time. The lipolytic action is confined to the phosphatide fraction of the plasma fats.

If there is delay between the addition of stypven and calcium, considerable amounts of lysophosphatides are produced which lengthen the clotting-time. More lipolysis occurs with lipæmic plasma than with fasting plasma, so that the accelerating effect of lipæmia on the clotting-time is partly masked by the lysophosphatides produced.

Stypven and calcium chloride are therefore better added simultaneously. Experiments with this "instantaneous" method on nine volunteers showed that the effect of fat feeding was consistent with all types of fat tried. Amounts as small as 14 g. had an appreciable effect, and larger amounts produced up to 50% shortening of the clotting-time. There was a significant positive correlation between the degree of lipæmia and the drop in stypven-time.

We are much indebted to the volunteers who cooperated in this study, to Dr. J. G. Humble for advice and criticism, and to Miss Naomi Dersch for technical assistance. The work was supported by generous grants from the endowment funds of Westminster Hospital.

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THYMIDINE IN MEGALOBLASTIC ANÆMIA

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Hausmann (1951) reported that two patients with pernicious anæmia showed maximal hæmopoietic responses to the intramuscular injection of between 100 and 250 mg. of thymidine daily until totals of 2·0 and 2·8 g. respectively had been given. Conversely, Rundles and Brewer (1958) did not obtain any hæmopoietic effect in one patient with pernicious anæmia who was given 500 mg. of thymidine daily for six days. Smaller doses of thymidine were found by Reisner and West (1949) to be ineffective in pernicious anæmia. Since the ability or otherwise of thymidine to produce hæmopoietic responses in pernicious anæmia has an important bearing on theories of the role of vitamin B_{12} and folic acid in blood formation in man, it was decided to investigate the problem further when suitable patients became available. We have been unable to demonstrate any significant hæmopoietic effect from the intramuscular injection of thymidine to five patients with pernicious anæmia in relapse and one patient with nutritional megaloblastic anæmia.

Methods and Materials

Chromatographically-pure thymidine, obtained from L. Light & Co., Ltd., or the Nutritional Biochemicals Corporation, U.S.A., was dissolved in pyrogen-free water at a concentration of 6·25 g. per 100 ml. The solutions were sterilised by autoclaving at 20 lb. pressure for 20 min. in rubber-capped containers. Microbiological assays with *Lactobacillus leichmannii* showed that thymidine was stable in solution under these conditions. Intramuscular injections of 4 ml. of these solutions, containing 250 mg. thymidine, were given to the patients once or twice daily for between 8 and 14 days. No untoward effects occurred as a result of the injections.

The patients studied were four men and one woman who fulfilled all the usual criteria for a diagnosis of addisonian pernicious anæmia in relapse, and one woman with megaloblastic anæmia due to dietary deficiency. Estimations of hæmoglobin, red blood-cells, and reticulocytes were carried out for several days before thymidine was given, to make sure that the patients were not showing spontaneous reticulocytoses

HÆMOPOIETIC RESPONSES TO THYMIDINE, VITAMIN B_{12}, AND FOLIC ACID IN PATIENTS WITH PERNICIOUS ANÆMIA (P.A.) AND NUTRITIONAL MEGALOBLASTIC ANÆMIA (N.M.A.)

Patient no.	Sex	Age	Anæmia	Treatments given	No. of days' treatment	Red-cell-count (millions per c.mm.)		Hæmoglobin (g. per 100 ml.)		Maximum reticulocytosis	
						Beginning	End	Beginning	End	%	Day observed
1	M	49	P.A.	(i) Thymidine 250 mg. daily (ii) Vitamin B_{12} 100 μg. daily for 6 days, then 100 μg. twice weekly	10 21	1·28 1·63	1·63 3·20	5·3 6·8	6·8 11·4	6·6 29·6	9 7
2	F	65	P.A.	(i) Thymidine 250 mg. b.d. (ii) Vitamin B_{12} 100 μg. daily	14 19	1·73 1·50	1·50 3·51	6·5 5·5	5·5 11·3	6·8 25·0	13 5
3	M	46	P.A.	(i) Thymidine 250 mg. b.d. (ii) Vitamin B_{12} 100 μg. daily	8 11	2·00 1·38	1·38 2·40	7·9 5·5	5·5 9·2	2·0 32·4	7 7
4	M	51	P.A.	(i) Thymidine 250 mg. b.d. (ii) Vitamin B_{12} 100 μg daily	11 11	2·13 1·83	1·83 2·81	9·0 8·8	8·8 11·6	5·4 12·4	2 6
5	M	55	P.A.	(i) Thymidine 250 mg. b.d. (ii) Vitamin B_{12} 100 μg. daily	9 11	1·75 1·74	1·74 2·45	7·4 6·6	6·6 9·3	2·2 22·8	4 5
6	F	74	N.M.A.	(i) Thymidine 250 mg. b.d. (ii) Vitamin B_{12} 100 μg. daily (iii) Transfusion, cells from 2 pints blood (iv) Vitamin B_{12} 100 μg. twice weekly, folic acid 15 mg. t.d.s., ascorbic acid 50 mg. t.d.s., full diet, and vitamins A, B complex, and D	10 6 — 36	2·76 1·80 — 2·71	1·80 1·85 — 3·70	9·2 6·4 5·6 8·2	6·4 5·6 8·2 12·9	1·6 1·8 — 29·4	3 4 — 6

or remissions. After satisfactory basal values had been established, the estimations were continued throughout the periods during which thymidine was given, and during the subsequent periods when the patients were treated with vitamin B_{12} or folic acid.

Results

The results are summarised in the accompanying table. With the exception of the first patient, the levels of red blood-cells and hæmoglobin remained stationary or fell during treatment with thymidine, and there was little or no evidence of reticulocytosis during this treatment.

The slight reticulocytosis in the second patient may not have been due to the thymidine, because this patient had shown a reticulocytosis of 9% on the seventh day before administration of thymidine was begun, although the reticulocyte-count had fallen to 2·6% by the time treatment with thymidine started.

The first patient showed small increases in the number of red blood-cells, and in the concentration of hæmoglobin, as a result of the treatment, as well as a small reticulocytosis on the ninth day of treatment. This response was suboptimal, however, and subsequent treatment with vitamin B_{12} caused a sharp rise in the reticulocyte-count and much larger increases in red blood-cells and hæmoglobin. All the other patients with pernicious anæmia showed similar responses when vitamin B_{12} was given after the thymidine. The patient with nutritional megaloblastic anæmia did not show any response to vitamin B_{12} during the short time that this was administered on its own, but she showed a response when folic acid, ascorbic acid, and other vitamins were given in addition.

Discussion

Our results show that in most patients with pernicious anæmia in relapse thymidine injected intramuscularly in doses of 250 or 500 mg. daily does not produce any hæmatological response. One patient with megaloblastic anæmia due to dietary deficiency also failed to show a response to thymidine. These observations agree with the findings of Rundles and Brewer (1958) in one patient with pernicious anæmia, and with those of Reisner and West (1949) in pernicious anæmia, using smaller doses of thymidine. Butterworth and Perez-Santiago (1956) were likewise unable to demonstrate any hæmopoietic response to the administration of thymidine in patients with tropical sprue. All these observations are in striking contrast to Hausmann's (1951) results, and the reason for this discrepancy is not clear. Hausmann's thymidine was prepared from liver and was only 85–90% pure, so that it seems possible that it may have contained enough vitamin B_{12} to produce hæmatological remissions in the doses given, even though 10 g. of the material gave a negative reaction for cobalt.

The almost complete failure of thymidine to show hæmopoietic activity is somewhat surprising in view of the reports (Spies et al. 1946, Spies and Stone 1947, Vilter et al. 1950) that thymine in large doses by mouth causes increased blood formation in pernicious anæmia. The amounts of thymine used were much greater than the doses of thymidine given in the present study, but since according to current theories (Vilter et al. 1950) thymidine is one step further along the chain of reactions leading to the synthesis of nucleoproteins, it might have been expected to be effective in smaller doses than thymine. It was impossible to give larger doses of thymidine because the maximum volume of fluid which can be injected intramuscularly at any one time without causing discomfort is about 4 ml., and the solubility of thymidine is such that only 250 mg. can be dissolved in this volume of water.

Our results appear to be in opposition to the hypothesis of Vilter et al. (1950) for the mechanism of blood formation in man. This hypothesis depends on the fact that thymine will produce therapeutic responses in patients with pernicious anæmia, even in cases which have become refractory to folic acid. It was inferred that folic acid promotes the synthesis of thymine from simple precursors and that vitamin B_{12} promotes the synthesis of thymidine from thymine. Rundles and Brewer (1958) have reported some therapeutic effects with orotic acid in pernicious anæmia and have suggested that this substance likewise may be a precursor of thymidine, though in fact they did not obtain any response to thymidine itself. L. G. Lajtha (personal communication) has found that thymidine has no effect on the maturation of megaloblasts in cultures of bone-marrow. While, therefore, the therapeutic effects of folic acid, orotic acid, and thymine in pernicious anæmia appear to be established, the key position of thymidine in the synthesis of nucleic acids in pernicious anæmia is open to question. Indeed, there appears now to be some doubt whether vitamin B_{12} does in fact act

by promoting the synthesis of nucleic acids (Lester Smith 1958).

Summary

Intramuscular injection of thymidine in doses of 250 mg. daily for 10 days was followed by a slight hæmopoietic response in one patient with pernicious anæmia in relapse, but doses of 500 mg. daily for between 8 and 14 days were without effect in four other patients with pernicious anæmia and in one patient with nutritional megaloblastic anæmia. All the patients responded promptly to treatment with vitamin B_{12} and folic acid respectively.

We wish to thank Miss Barbara Mallett, B.SC., for the hæmatological examinations on the patients.

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PATHOLOGY AND TREATMENT OF MAMMARY-DUCT FISTULA

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IN 1955, Atkins for the first time in this country described under the title of "mammillary fistula" a common and troublesome recurrent infective condition of the breast. He showed that the condition was a fistula of a large mammary duct near the nipple, and advised treatment by exteriorisation on the same principles as the standard treatment of fistula-in-ano. According to Atkins, the fistulous nature of the condition was first recognised in 1951 by Zuska et al., who described 5 cases under the title of "fistulas of lactiferous ducts". There is also a paper by Kilgore and Fleming (1952).

Our interest in the condition was first aroused by Atkins' paper; we have, however, treated it on different lines. Instead of exteriorising the fistula, we have excised it complete up to the opening of the involved duct at the nipple. The material obtained in this way has been studied pathologically, and our findings are here recorded.

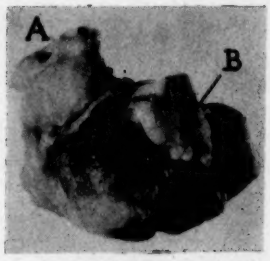

Fig. 1—Operation specimen (life size) showing ellipse of skin surrounding opening of granulating track (B). In the left upper part of the specimen is the cylinder of tissue from the nipple itself (A).

Clinical Features

We have treated 7 cases, and the clinical features are similar to those noted by Atkins.

Our youngest patient was 24 and had had no children; our oldest, who was 48, had had 2 children. The condition was associated with some degree of retraction of the nipple in 6 out of the 7 cases. The typical history is of the development of a lump eccentrically situated under the areola, sometimes but not always with the clinical features of an abscess. The abscess either ruptures or is opened and drained, but does not permanently heal. Periods of apparent healing, which may be of long duration, alternate with periods of discharge from a small granulating orifice situated at the margin of the areola. In 1 of our patients this history extended over twenty years. There is usually a history of multiple operations and of various types of chemotherapy. In another patient a diagnosis of tuberculosis had been made as a result both of the histological examination and of the finding of "tubercle bacilli", and she was in the middle of a prolonged course of antituberculous chemotherapy which was having no effect. Histologically, the lesion proved to be a chronic granuloma and the "tubercle bacilli" to be atypical acid-fast bacilli, akin to smegma bacilli.

Pathological Study

The specimens (fig. 1) consisted of the externally draining granulating orifice of the fistula with a small margin of surrounding skin; a core of tissue surrounding the track up to the nipple; and, in a few cases, a small portion of nipple skin. The specimen was divided into blocks and serial histological sections cut.

Fistulous Track

This portion of the track was always found lined by non-specific granulation tissue. In no case had squamous epithelium grown down from the margins of the orifice more than a very short distance. At varying distances from the external opening, the track lined by granulation tissue communicated in all cases with one of the main subareolar mammary ducts.

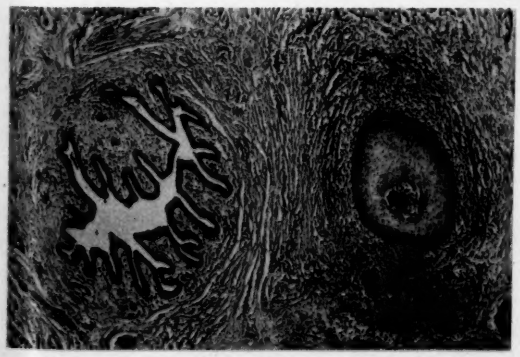

Fig. 2—A normal lactiferous duct from the ampullary region with its characteristic star-shaped outline, and alongside it a duct with a squamous lining and keratin plug (×33).

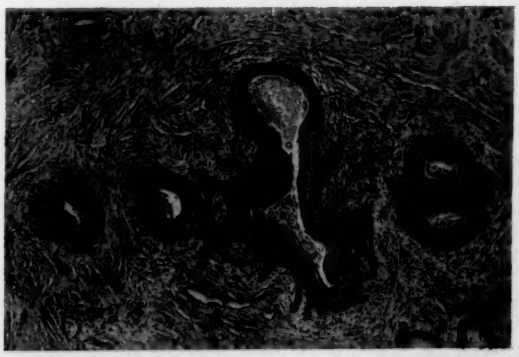

Fig. 3—Branching of a squamous duct in the nipple; the lumen of both main duct and side branches is full of laminated keratin (×33).

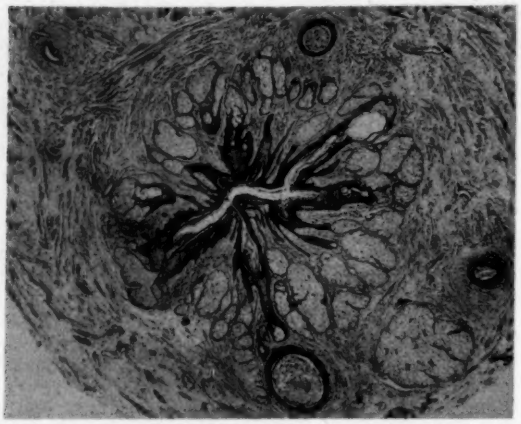

Fig. 4—Squamous lined duct at level of base of nipple, showing large numbers of sebaceous glands and also branching (×21).

Mammary Ducts

The ampullary portion of the 30 or so normal mammary ducts under the nipple have, when collapsed, a characteristic star-shaped outline on histological examination (fig. 2). Under higher power, a double layer of lining epithelial cells can be seen, the inner of columnar epithelium and the outer of flattened myoepithelium. In contradistinction to the normal appearance, the duct with which the granulating track communicated was in 6 of our 7 cases lined by stratified squamous epithelium (figs. 2 and 3). In 5 of the 6, the squamous epithelium extended the whole way from the nipple to the bottom of the granulating track. In the 6th case, the squamous-lined duct extended only a part of the way from the nipple, after which it was replaced by a column of granulation tissue in which keratin scales could be recognised. In the 7th case, the course of the duct could be traced to the nipple, but there was no epithelium, the duct being represented entirely by granulation tissue.

In only 1 case was there a patent lumen in that part of the duct lined by squamous epithelium; in the others the duct was full of cornified epithelial cells forming an obstructing plug (fig. 2). Sometimes the squamous duct showed branching (fig. 3), and these squamous-lined branches when traced distally eventually showed an abrupt transition to normal epithelium. In two specimens there were sebaceous glands discharging into the duct; in one these were numerous (fig. 4) and extended the whole distance to the point of communication with the fistulous track, where the abnormal duct was distended to form a sebaceous cyst. Inflammatory changes when present around the duct were minimal. Fig. 5 represents diagrammatically the typical pathological features.

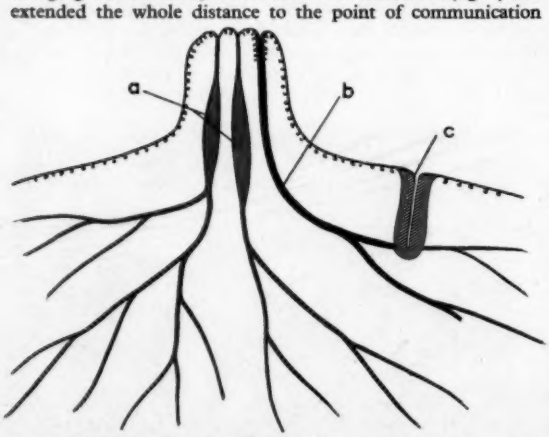

Fig. 5—Diagrammatic sagittal section of nipple to indicate (a) normal ducts lined by columnar epithelium and myoepithelium, (b) abnormal squamous lined duct, and (c) fistula lined by inflammatory granulation tissue. Sebaceous glands in skin and upper part of squamous duct are also indicated.

In one specimen there were a few hairs free in the duct lumen, but no hair follicles could be found on serial sectioning. It was presumed, therefore, that the hairs had entered through the orifice of the duct. Similar free hairs have also been found in the lumen of a main lactiferous duct of a normal nipple, again no hair follicles being present. This phenomenon, which we have not seen recorded previously, is analogous to the entry of hairs postulated in the acquired theory of pilonidal sinus, and presumably the hairs enter as a result of the same frictional mechanism (Patey and Scarff 1955).

Discussion

Pathology

Our findings confirm those of Zuska et al. and of Atkins in demonstrating that the condition is a mammary-duct fistula. The demonstration of an abnormal duct lined by squamous epithelium in 6 out of 7 cases would suggest some close relation of this feature to the pathology of the condition. Theoretically, the squamous lining might be either a cause or an effect of the inflammatory condition. Squamous epithelium often does grow down to line granulating tracks. In the present material, however, this explanation can be excluded, since in all cases the externally opening track was shown to be lined purely by granulation tissue. Another possibility is that of squamous metaplasia of the epithelium normally lining the affected duct as a result of the chronic infection. This possibility cannot be excluded, but against it is the slight active inflammation around the duct, and the fact that closely adjacent main ducts are unaffected (fig. 2). Drainage of inflammatory matter does not usually occur by way of the nipple in these cases, whereas the squamous epithelium extends not only to the nipple, but also into tributaries of the affected duct which are away from the region of the inflammatory process.

The remaining possibility is that the abnormal duct is a primary congenital abnormality. This must certainly be so in the one case of the duct with multiple sebaceous glands illustrated in fig. 4. Either, therefore, the condition is always due to a congenital abnormality of one of the main mammary ducts; or some cases are congenital and some are acquired, in the latter case the squamous change in the duct resulting from metaplasia. On the whole, we are inclined to favour the congenital theory. We are at present investigating the duct structure of the nipple of normal postmortem subjects, and this may give further evidence on this point.

On either the congenital or acquired theories, the squamous-lined duct probably plays an important role in the persistence of the infection. The presence of plugs of keratin must interfere with drainage, and it is well known that infections and resulting discharging sinuses involving epithelial-lined tracks rarely clear up until the track is either completely excised or is marsupialised.

Treatment

The frequency of an abnormal duct, whether congenital or acquired, is in favour of treatment by extirpation, including the removal of the affected duct, rather than by a simple drainage procedure as advocated by Atkins. Kilgore and Fleming (1952) also advise excision. A decision on this point will have to be determined by long-term results. The obvious disadvantage of excision is that other main mammary ducts besides the affected duct are necessarily removed, with the likelihood of interference

with the function of the breast should the patient subsequently lactate. In older women this argument does not of course apply. But even in younger women, the worry caused by a persistent discharging lesion of the breast is so great that, should excision prove to be a better operation than exteriorisation, this might outweigh the disadvantages of possible interference with lactation.

Summary

Mammary-duct fistula is a common cause of persistent or recurrent inflammation and discharge following a periareolar abscess.

Histological studies show that the condition is associated with a duct lined with squamous epithelium, in contradistinction to the normal lactiferous ducts which are lined by two layers of cells, the inner columnar epithelium and the outer flattened myoepithelium.

In some cases, the presence of sebaceous glands opening into the abnormal duct points to a congenital abnormality. In others, the abnormal lining of the duct may result from squamous metaplasia; there is, however, evidence against this view and all cases may represent a congenital abnormality.

The rational radical treatment is complete excision of the fistula and the abnormal duct; if exteriorisation proves in practice to be equally satisfactory, it may be preferable as interfering less with the normal ducts of the nipple.

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ACUTE MYOCARDIAL ISCHÆMIA: SIGNIFICANCE OF PLASMA-TRANSAMINASE ACTIVITY*

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PATIENTS with ischæmic heart-disease commonly have episodes of cardiac pain which differ from those of angina pectoris in that the pain lasts for from many minutes to several hours and is unrelieved by rest or nitrites. Attacks of pain may be single or frequently repeated. The clinical or electrocardiographic (E.C.G.) features of acute myocardial infarction do not develop. These episodes have been variously termed " acute coronary insufficiency " (Master 1944), " coronary failure " (Freedberg et al. 1948), " minor coronary attacks " (Papp and Smith 1951), " intermediate coronary syndrome " (Graybiel 1955), " acute atypical coronary artery insufficiency " (Littman and Barr 1952). Attention is thereby focused on the coronary arteries and not upon the myocardium.

It is recognised that patchy or focal areas of myocardial necrosis may occur, even to the extent of " subendocardial infarction " (Horn et al. 1950). The underlying abnormality is believed to be severe but transient myocardial ischæmia. Added weight has been given to this belief by reports of normal glutamic oxalacetic transaminase (G.O.T.) activity of serum in patients with " acute coronary insufficiency " (La Due and Wroblewski 1955, Nydick et al. 1957) and in " the anginal syndrome " (Chinsky et al. 1956).

G.O.T., being in high concentration in heart-muscle, is much increased in serum or plasma after clinical and experimental myocardial infarction (La Due et al. 1954, Nydick et al. 1955), but after experimental temporary myocardial ischæmia there is no such increase (Nydick et al. 1957).

We describe here the results of serial estimations of glutamic oxalacetic transaminase activity of plasma (P.G.O.T.) in 18 patients with severe episodes of cardiac pain, unassociated with clinical and E.C.G. evidence of recent myocardial infarction.

Materials and Methods

All patients had one or more attacks of severe typical cardiac pain lasting longer than fifteen minutes and not relieved by rest or trinitrin. Fever, leucocytosis, persistently reduced blood-pressure, friction rub, or cardiac failure did not ensue. E.C.G. changes were limited to depression of S–T segments and flattening or inversion of T waves. Patients with previous known myocardial infarction who had abnormal Q waves were admitted to the series provided the appearances were unchanged from previous E.C.G.s. No patient had had myocardial infarction during the previous three months. All patients rested in bed and received heparin by injection for two days and oral phenylindanedione. Morphine sulphate gr. $^1/_4$ or $^1/_6$ was given when trinitrin gr. $^1/_{100}$ failed to relieve pain.

P.G.O.T. assay was performed by a modification (E. N. O'Brien and A. J. Goble, unpublished) of the spectrophotometric method of Karmen (1955). Normal values for this laboratory are 5–28 units with a mean of 11 and S.D. $\pm$4. Serial P.G.O.T. levels were obtained on all patients for at least seven days. For comparison, serial P.G.O.T. levels were obtained, for periods of five to twenty days, from 25 normal subjects and from 20 patients with a history of angina pectoris or previous myocardial infarction, who were at rest in hospital and free from pain.

Erythrocyte-sedimentation rate (E.S.R.) was estimated using Westergren tubes and dry sodium oxalate as anticoagulant. Normal values are 1–10 mm. in the first hour for males and 1–15 mm. for females.

Results

Normal Subjects and Pain-free Patients

In 24 out of 25 normal subjects, the individual highest-to-lowest range of P.G.O.T. levels, estimated over five to twenty days, was 10 units or less. In 1 subject the maximum range was 13 units. In all 20 patients with known ischæmic heart-disease, the individual maximal range of P.G.O.T. levels estimated over five to twenty days was less than 10 units. Representative patterns of serial P.G.O.T. levels are shown in fig. 1.

Patients with Pain

10 patients had isolated attacks of cardiac pain (table I). 4 of these (cases 1–4) had E.C.G. changes limited to depression of S–T segments and T-wave inversion. In

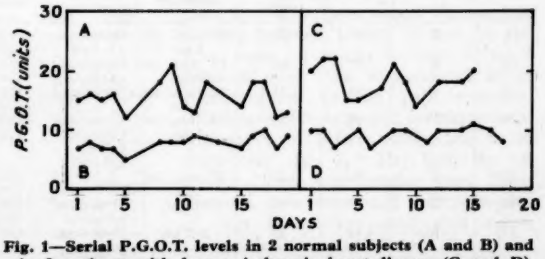

Fig. 1—Serial P.G.O.T. levels in 2 normal subjects (A and B) and in 2 patients with known ischæmic heart-disease (C and D). (Maximum ranges of P.G.O.T.: A, 9 units; B, 5 units; C, 8 units; D, 4 units.)

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TABLE I—FINDINGS IN 10 PATIENTS WITH ISOLATED EPISODES OF CARDIAC PAIN

Case no.	Sex	Age (yr.)	Pain			B.P. (mm. Hg)	E.C.G.		E.S.R. (Westergren) max. (mm. in 1st hr.)	P.G.O.T. max. range (units)
			Duration	Recurrence	Associated phenomena		ST and T changes	Unchanged infarction		
1	M	49	2 hr.	—	Dyspnœa, sweating	155/90	aVL V_{5-6}	—	6	5 (20–15)
2	M	41	2 hr.	—	—	180/120	aVL V_{1-4}	—	2	7 (15–8)
3	M	55	20 min.	5 days	Dyspnœa, sweating	150/90	I V_{5-6}	—	31	31 (42–11)
4	F	68	2 hr.	5 days	Dyspnœa, sweating, pallor, B.P. fall	140/85	V_{1-2}	—	60	37 (49–12)
5	M	84	30 min.	—	—	130/80	—	Rt. bundle-branch block	6	7 (21–14)
6	M	53	30 min.	—	Dyspnœa, nausea, syncope	135/80	—	Posterior	4	3 (12–9)
7	M	50	1 hr.	4 days	Dyspnœa	150/90	—	Posterior	5	6 (20–14)
8	M	64	3 hr.	—	Dyspnœa, sweating, angor animi	140/100	—	Posterior	10	4 (12–8)
9	M	53	2 hr.	—	Sweating	150/90	—	Posterior and anteroseptal	25	21 (31–10)
10	M	74	30 min.	—	—	130/80	—	Posterior	22	16 (30–14)
			30 min.	—	—	130/80	V_{4-6}	Posterior	26	65 (75–10)

cases 1 and 2, P.G.O.T. activity remained normal for ten days (fig. 2). In case 1 myocardial infarction occurred on the twelfth day. In cases 3 and 4 there was an abnormal rise in P.G.O.T. activity, which rapidly returned to normal (fig. 3). The other 6 patients (cases 5–10) had old unchanged infarction patterns in the E.C.G. In 4 (cases 5–8) there was no rise in P.G.O.T. activity (fig. 2), while in 2 (cases 9 and 10) there was an early abnormal rise in P.G.O.T. activity and rapid return to normal (fig. 3). Case 10 had a second episode of pain after twelve days associated with a second larger abnormal rise in P.G.O.T. level.

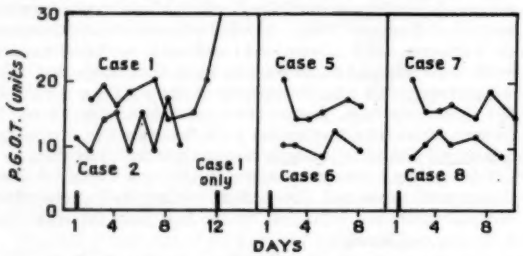

Fig. 2—Serial P.G.O.T. levels in 6 patients with isolated severe episodes of cardiac pain. Lines indicate timing of pain episodes. Note normal variation in serial P.G.O.T. levels. Second attack of pain in case 1 was associated with obvious myocardial infarction and P.G.O.T. rise to 205 units.

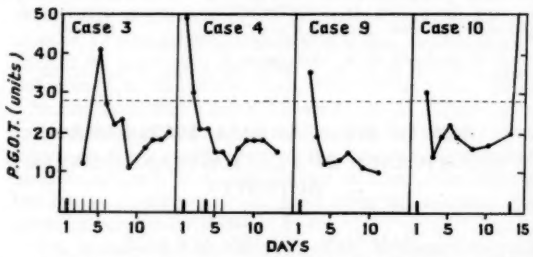

Fig. 3—Serial P.G.O.T. levels in 4 patients with isolated episodes of severe cardiac pain. Long attacks of pain are indicated by heavy lines and minor attacks by fine lines. Dotted line at 28 P.G.O.T units indicates upper limit of normal. Note delayed rise in P.G.O.T. level in case 3.

8 patients had recurrent attacks of cardiac pain for two weeks or more (table II). 4 of these (cases 11–14, fig. 4) had E.C.G. changes limited to S–T depression and T-wave inversion, while 4 (cases 15–18, figs. 4 and 6) had unchanged old infarction patterns. In all cases there were intermittent or irregular rises in P.G.O.T. activity to abnormal levels. In case 11, four small rises in P.G.O.T. activity were associated with severe attacks of pain. During the fourth episode, with minor P.G.O.T. rise, the E.C.G. changed to an acute posterior infarction pattern (fig. 5). In case 12 two small rises in P.G.O.T. level occurred after long attacks of pain. In cases 13 and 14, P.G.O.T. rises were associated with initial severe episodes

TABLE II—FINDINGS IN 8 PATIENTS WITH RECURRENT EPISODES OF CARDIAC PAIN

Case no.	Sex	Age (yr.)	Total period of pain (days)	Long-continued pains		B.P. range (mm. Hg)	E.C.G.		E.S.R. (Westergren) max. (mm. in 1st hr.)	P.G.O.T.	
				Duration	Associated phenomena		ST and T changes	Unchanged infarction		Peaks	Max. range (units)
11	F	46	57	30 min. to 6 hr.	Dyspnœa, B.P. fall	160/110–140/90	I, II, aVL aVF, V_{5-6}	—	52	30, 42, 40, 24–29	33 (42–9)
12	F	57	61	15 min. to 4 hr.	Dyspnœa, sweating	165/90–140/70	I, aVL V_{5-6}	—	41	22, 25	16 (25–9)
13	F	54	31	30 min. to 1 hr.	Sweating	170/100–150/90	I, II, aVL V_{5-6}	—	48	41, 45, 35, 44	25 (45–20)
14	M	64	21	30 min. to 3 hr.	Dyspnœa, sweating, pallor, B.P. fall	150/90–120/80	I, aVL V_{5-6}	—	60	30, 32, 36, 30–34, 28	22 (36–14)
15	F	50	20	20 min. to 2 hr.	—	120/80–110/80	—	Anterior	10	25, 35, 25	25 (35–10)
16	F	65	45	1–3 hr.	Dyspnœa, sweating	130/80–120/80	—	Posterior	42	42	32 (42–10)
17	M	71	35	2–5 hr.	Dyspnœa, sweating, pallor	150/90–130/80	V_{5-6}	Posterior	90	30, 29, 75, 30	62 (75–13)
18	F	59	51	2–3 hr.	Sweating, B.P. rise	145/90–130/85	—	Anterior	45	127, 50, 109, 104	117 (127–10)

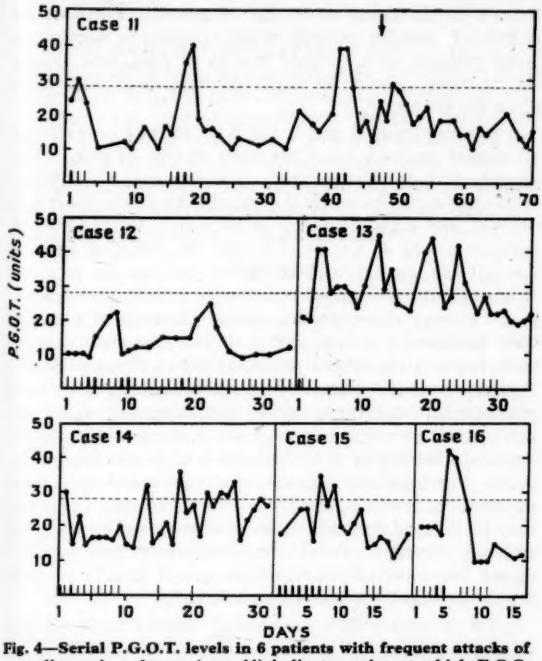

Fig. 4—Serial P.G.O.T. levels in 6 patients with frequent attacks of cardiac pain. Arrow (case 11) indicates point at which E.C.G. changes of acute posterior myocardial infarction appeared (see fig. 5). Note delayed rise of P.G.O.T. levels in cases 13 and 14.

of pain, but also occurred later when the only complaint was of intermittent minor attacks of pain and persistent heaviness in the chest. In case 17 a period of irregular variation in P.G.O.T. levels was followed by a sharp rise associated with an episode of recurrent long attacks of pain extending over three days (fig. 6). Case 18 had four sharp rises in P.G.O.T., each associated with a severe long attack of pain (fig. 6); a fifth similar attack of pain was not followed by P.G.O.T. rise. Between the third and fourth P.G.O.T. rise the E.C.G. changed to a persisting left-bundle-branch-block pattern.

E.S.R. remained normal in all patients in whom no rise in P.G.O.T. occurred, but became increased in 11 of the 12 patients with raised P.G.O.T. levels.

In those patients in whom a rise in P.G.O.T. level was closely related to pain, and hence to the administration of morphine, there was no P.G.O.T. rise after a later injection of morphine.

Case-reports

Case 1.—A taxi-driver, aged 49, developed constricting chest pain radiating down both arms, lasting fifteen minutes, while sitting in his cab. Next day while he was eating breakfast a similar severe attack of pain occurred; this lasted two hours, and was eventually relieved by morphine.

Physical examination four hours later was normal, with blood-pressure (B.P.) 155/90 mm. Hg. During the next ten days he remained symptom-free with normal examination findings. Serial E.C.G.s revealed varying T-wave inversion in leads aVL and V_{2-6}. E.S.R. and P.G.O.T. remained normal. On the eleventh day severe pain developed, with tachycardia, B.P. fall, dyspnœa, and sweating. Next day his temperature was 101·8°F, E.C.G. revealed anteroseptal infarction, and P.G.O.T. rose to 205 units (fig. 2).

Case 3.—An obese policeman, aged 55, gave a six-week history of mild angina of effort. Eighteen hours before admission he was awakened by severe constricting chest pain radiating to the left arm, associated with dyspnœa and sweating, and lasting twenty minutes.

Physical examination was normal. He remained well, but noticed intermittent vague chest discomfort and slight chest pain on movement during the next five days. Repeated E.C.G.s revealed variable S–T depression and T-wave inversion in leads 1 and V_{2-4}. E.S.R. rose to 31 mm. in the first hour on the fourteenth day. P.G.O.T. activity thirty hours after the onset of pain was normal, rising to 42 units on the third day, and returning rapidly to normal (fig. 3).

Case 11.—An obese 46-year-old housewife gave a history of a severe attack of cardiac pain eighteen months previously. She was admitted to hospital after six days of repeated severe and long attacks of constricting chest pain, radiating to the left arm. She had three further long bouts of severe pain while in hospital, with interspersed milder pain, relieved by trinitrin. Heaviness in the chest continued until the end of the final episode of pain fifty-one days after admission.

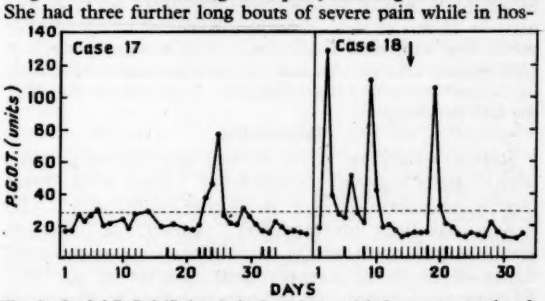

Fig. 6—Serial P.G.O.T. levels in 2 patients with frequent attacks of cardiac pain. Arrow (case 18) indicates point at which E.C.G. changed to left-bundle-branch-block pattern.

Physical examination revealed a heart-rate of 105–90 per min. and a presystolic triple rhythm; both persisted for fifty-one days. B.P. falls to 120/80–70/50 mm. Hg occurred with some severe attacks of pain; B.P. otherwise remained at 160/110–140/90 mm. Hg until, following the final episode of severe pain, it remained at about 130/80 mm. Hg. During the final fifteen days in hospital, physical examination was normal. E.C.G.s revealed S–T depression and T-wave inversion in leads 1, 2, aVL, aVF, and V_{3-6}. These changes persisted until, following an episode of severe pain on the forty-sixth day, a posterior-infarction pattern appeared with deep Q waves and S–T elevation in leads III and aVF (fig. 5). E.S.R. was raised throughout, varying between 13 and 52 mm. in the first hour. P.G.O.T. activity revealed transient peak rises to abnormal levels corresponding to the pain episodes. The rise which occurred simultaneously with the E.C.G. infarct pattern was to 24 units only (fig. 4). The final rise in P.G.O.T. level was smaller than three previous rises associated with episodes of pain but unassociated with E.C.G. changes indicating infarction.

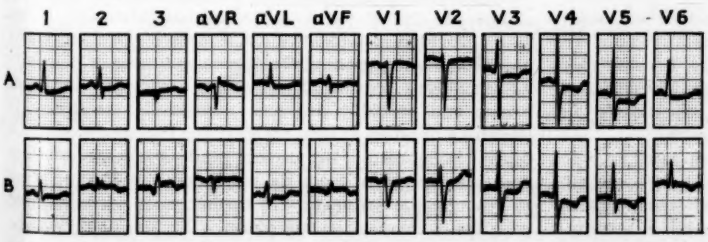

Fig. 5—E.C.G. of case 11. Tracing A is ischæmic pattern which persisted until 46th day. Tracing B is pattern of posterior infarction which appeared on 47th day, after final long attack of pain (see fig. 4).

Case 13.—A 54-year-old obese housewife gave a history of six months'

angina of effort. On the day before admission she had three attacks of severe retrosternal crushing pain with sweating. The pains lasted from thirty minutes to an hour, occurred at rest, and were unrelieved by trinitrin. Two further attacks of long-continued severe pain occurred on the day of admission; and intermittent attacks of milder pain, relieved by trinitrin, occurred during the next thirty-five days. A feeling of heaviness in the chest persisted throughout.

Physical examination remained unchanged, with B.P. ranging between 170/100 and 150/90 mm. Hg. E.C.G.s showed variable S–T depression and T-wave inversion in leads 1, 2, aVL and V_{3-6}. E.S.R. rose to 44 mm. in the first hour after seven days, P.G.O.T. activity rose on four occasions to peaks of 41, 45, 35, and 44 units (fig. 4).

Case 18.—A 59-year-old housewife gave a history of myocardial infarction two years previously and three months previously. For three weeks she had increasingly frequent and severe attacks of constricting chest pain radiating to the right arm, occurring both at rest and on slight effort. Five attacks of long-continued pain associated with sweating occurred during the first twenty days in hospital. There were intermittent frequent minor attacks of chest pain relieved by trinitrin.

Examination findings remained normal throughout with B.P. ranging from 145/90 to 130/85 mm. Hg. During attacks of severe pain the B.P. rose slightly; the pulse-rate remained normal. E.C.G. revealed previous anterior infarction pattern until, between the third and fourth attacks of pain, left-bundle-branch-block pattern appeared and persisted. E.S.R. ranged between 15 and 45 mm. in the first hour, but fell to 10 mm. in the first hour after thirty days. P.G.O.T. activity revealed peak rises to 127, 50, 109, and 104 units on the day after each of the first four severe attacks of pain. There was no rise after the fifth attack (fig. 6).

Discussion

Reports of normal G.O.T. activity in serum of patients with "acute coronary insufficiency" have been based largely on intermittent or occasional estimations. The results have been interpreted as "normal" or "borderline" because the readings have fallen below an arbitrary figure of 48 or 50 Karmen units (Ostrow et al. 1956, Chinsky et al. 1956). In the present study of 25 normal subjects and 20 patients with known ischæmic heart-disease who were resting and free from pain, the individual maximum range of serial P.G.O.T. levels was 10 units or less with 1 exception. Rises of P.G.O.T. levels beyond an individual highest-to-lowest range limit of 15 units are therefore regarded here as abnormal, and between 10–15 units as probably abnormal. Thus, in case 12, the rises in P.G.O.T. level to 22 units and 25 units, from a lowest recorded reading of 9 units, are presumed to indicate minor episodes of myocardial necrosis (fig. 4).

Of the 18 patients with long-continued typical cardiac pain, there were 12 with increased P.G.O.T. levels; but this increase was small in most cases. There was a subsequent rise in the E.S.R. in 11 of these. This suggests that P.G.O.T. activity is a much more sensitive index of myocardial necrosis than was hitherto realised.

That small rises in P.G.O.T. levels can indicate structural myocardial damage is illustrated by case 11 where an ischæmic E.C.G. pattern finally changed to a pattern of posterior myocardial infarction, with deep Q waves and S–T elevation in leads III and aVF, following a rise in P.G.O.T. level from 12 to 24 units (figs. 4 and 5).

Of the 10 patients with isolated attacks of pain, a single rise in P.G.O.T. activity occurred in 4 (cases 2, 3, 9, and 10, figs. 2 and 3). In case 10 a second isolated attack of pain was followed by a second larger rise in P.G.O.T. activity. The 8 patients with repeated attacks of pain extending over more than two weeks all had irregular or repeated rises in P.G.O.T. levels (cases 11–18, figs. 4 and 6). The patterns of P.G.O.T. activity indicate single episodes of necrosis in some patients with isolated attacks of pain, and similar but repeated episodes in those with attacks of pain which recur for weeks.

6 patients (cases 1 and 2 and 5–8) showed no evidence of muscle necrosis following their attacks of pain. The severity and duration of their pain appeared no different from that experienced by the patients in whom there was P.G.O.T. and E.S.R. evidence of necrosis. Furthermore 5 patients (cases 4, 12, 14, 17, and 18), without ensuing P.G.O.T. rise, experienced attacks of pain, similar in duration and severity to those which were followed by P.G.O.T. rise. During these attacks, which occurred at rest and were unrelieved by trinitrin, both dyspnœa and sweating occurred and sometimes profound fall in blood-pressure. Prolonged severe pain, even with disturbing associated phenomena, therefore does not denote significant myocardial necrosis, but suggests prolonged myocardial ischæmia, during or following which muscle necrosis may occur. Furthermore, demonstrable myocardial necrosis is not necessarily related closely to severe episodes of pain but may be delayed for days (case 3) or even weeks (cases 13 and 14), during a period when the patient may notice a vague heaviness in the chest or minor attacks of pain which are rapidly relieved by trinitrin.

Of 8 patients with E.C.G. changes limited to depression of S–T segments and inversion of T waves (cases 1–4 and 11–14), myocardial necrosis occurred in 6, judged by P.G.O.T. activity and increase in E.S.R.; but there was no evidence of necrosis in 2 patients (cases 1 and 2) with similar E.C.G. patterns. This suggests that these electrocardiographic changes are produced by considerable myocardial ischæmia, rather than by the necrosis which commonly ensues.

Of the 10 patients who showed E.C.G. evidence of old myocardial infarction (cases 5–10 and 15–18) there were rises in P.G.O.T. levels in 6 without any alteration in the E.C.G.; but in the second episode of pain in case 10 and the long attack of pain in case 17 (fig. 6) S–T depression was associated with rises in P.G.O.T. to 75 units and 76 units respectively. In case 18 (fig. 6), P.G.O.T. activity rose to 125, 50, and 109 units with the E.C.G. remaining unchanged. Before a further rise to 104 units, the E.C.G. changed to a left-bundle-branch-block pattern, this being the first E.C.G. evidence of extending myocardial infarction. This suggests, therefore, that extensive myocardial necrosis may occur before any new changes appear in the E.C.G. pattern of previous infarction.

In none of the 18 patients did the temperature rise, or leucocytosis, persistent fall in blood-pressure, or cardiac failure develop. The E.C.G. revealed depression of S–T segments or inversion of T waves, whether necrosis was demonstrable or not, and was unreliable in the presence of changes due to previous myocardial infarction. The E.S.R. provided a guide to muscle necrosis, but supplied no information regarding the degree or timing of necrosis. P.G.O.T. levels, estimated daily, are a sensitive index of timing and probably degree of myocardial necrosis. It therefore provides a new method for the study of myocardial ischæmia. That further study by this method is necessary is evident from the confusion in the terms used to describe the syndromes of cardiac pain not associated with frank myocardial infarction. Terms including the word "coronary" are based on concepts which cannot be confirmed short of necropsy.

A new descriptive terminology is both possible and necessary, recognising that cardiac pain, irrespective of its duration or severity, indicates myocardial ischæmia, that rises of E.S.R. and P.G.O.T. levels indicate myocardial necrosis, and that the E.C.G., if it alters, indicates the localisation of the myocardial ischæmia or necrosis. It should also be recognised that repeated small episodes of myocardial necrosis may summate to produce the E.C.G. pattern of transmural myocardial infarction.

Summary

Plasma-glutamic-oxalacetic-transaminase activity is a sensitive index of myocardial necrosis.

18 patients with severe cardiac pain, not associated with frank myocardial infarction, were studied by serial estimations of plasma-transaminase activity.

In 12 there was evidence of single or repeated episodes of myocardial necrosis.

The severity and duration of pain, associated dyspnœa, sweating, and temporary fall in blood-pressure, and electrocardiography are unreliable guides to necrosis associated with severe myocardial ischæmia.

Concepts and descriptive titles of the ischæmic episodes which occur with coronary-artery disease need to be reviewed in the light of transaminase activity.

We wish to thank Miss B. Paterson for assistance with the transaminase assays, the honorary physicians of the Royal Melbourne Hospital for referring patients, Dr. C. H. Fitts for his encouragement and constructive criticism, and Prof. R. R. H. Lovell for making available laboratory facilities in the University of Melbourne Department of Medicine at the Royal Melbourne Hospital.

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PROTEIN METABOLISM DURING CORTICOSTEROID THERAPY

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SHEFFIELD CENTRE FOR THE INVESTIGATION AND TREATMENT OF RHEUMATIC DISEASES

ALMOST every published account of the physiological effects of cortisol includes the statement that it is a protein-catabolic and/or a protein-anti-anabolic hormone. Reifenstein (1958), contributing to a symposium on adrenocortical steroids, stated that all patients receiving maintenance therapy should be given at the same time a protein-anabolic hormone (i.e., a testosterone derivative).

Nevertheless it is common experience to see patients increase in strength as well as in weight during treatment with cortisol or one of its analogues. This may be seen equally well during the treatment of certain wasted rheumatoid-arthritic patients as during the treatment of a patient with Addison's disease.

At this centre a great number of twenty-four-hour urinary creatinine estimations have been made as a check on the completeness of urinary collection made for other purposes. Those made on patients receiving prolonged corticosteroid therapy have been reviewed for the evidence they provide of changes in muscle mass, the main protein store, during such therapy.

That the excretion of creatinine may be taken to reflect the muscle mass of a patient is based on three observations: (1) that creatinine excretion is directly proportional to the amount of creatine in the body (Hoberman et al. 1948); (2) that 98% of the body's creatine is in the skeletal muscles (Bodansky and Bodansky 1952); (3) that in no chronic disease state have changes in excretion of creatinine been shown to be at variance with changes in muscle mass. A possible exception is acromegaly (Scherere 1937). Most of the patients in the present study were treated with corticotrophin. The corticotrophin used contained no growth hormone, and if it had it would not have been effective since the corticotrophin was of bovine and porcine origin. There is no evidence that either adrenocortical stimulation with corticotrophin or orally administered prednisolone gives rise either directly or indirectly to growth-hormone effects.

Methods and Material

Measurement of Creatinine Excretion

The method used was that described by Delory (1949). This method has been shown to measure creatinine accurately within the range of levels likely to be encountered in the patients studied. The reaction involved is not specific for creatinine in urine. The interfering substances are ketones and keto-acids, and ascorbic acid (Taussky 1954). During the control periods referred to in table I some of the patients may have had a mild ketosis, and all of them did have 150 mg. of ascorbic acid daily; but from the observations of Spanner and Boscott (1956) the amounts appearing in the urine were not likely to have been sufficient to appreciably affect the assay. If they had had an effect it would have been to increase the apparent output of creatinine and so reduce the magnitude of any later rise in output.

The small day-to-day variations in creatinine excretion found even with the most exact collecting of twenty-four-hour specimens necessitates the collection of many specimens to establish a reliable mean. Even with many specimens the results may not be reliable if the patient is not conscientious in making the collections. The records of some patients have been excluded from the present analysis because of obvious inconsistencies in their collecting habits.

The Corticosteroid Therapy

Cortisone acetate was given in a dose of 50 mg. or more. A maintenance dose of 50 mg. of cortisone acetate given in divided doses may not be enough to affect the metabolism of a large person. The only patient who had this dose weighed only 46–54 kg. Prednisolone was given in a dose of 12·5 mg. or more. Although 12·5 mg. a day may not completely suppress endogenous cortisol production it certainly effects metabolic changes even in a large person. The dosage of corticotrophin, given by daily intramuscular injection, was such as to raise the urinary output of 17-ketogenic steroids (Norymberski et al. 1953) or total 17-hydrocorticosteroids (Appleby et al. 1955) 100–200% above control levels. This reflects a similar increase in the daily secretion of cortisol by the adrenal glands. That the required level was maintained was ensured by repeated urinary assays and adjustments of dose. To be precise in the matter of dosage, the mean effective level of the corticosteroid in the plasma should be stated whatever the route of administration. Unfortunately this cannot yet be done as the effective level is determined by the degree of protein binding of the substance in the plasma, and no method for estimating this is suitable for routine use. From the work of Daughaday (1958) it seems that doubling of the normal adrenal output of cortisol

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TABLE I—MEAN CREATININE EXCRETION, MEAN DOSE, AND MEAN BODY-WEIGHT RECORDED DURING LONG-CONTINUED CORTICOSTEROID THERAPY

Case no.	Sex	Age (yr.)	Diagnosis	Duration of disease (yr.)	Period (mos.)	Therapy	Mean daily dose (mg.) †	Mean creatinine excretion per 24 hr. (mg.)	Standard deviation ‡	Mean weight (kg.)	Creatinine coefficient §
1	F	35	R.A.	3	Control	—	—	1·39	0·07	64·5	21·5
					1–6	Corticotrophin	29	1·56•	0·05	69	22·5
2	F	51	R.A.	2	Control	—	—	0·91	0·08	42·5	21·5
					1–8	Corticotrophin	25	1·05•	0·05	50·5	21
					9–16	„	22	1·01	0·06	51·5	19·5
3	M	43	R.A.	½	Control	—	—	1·57	0·04	68·5	23
					1–12	Corticotrophin	24	1·63•	0·095	78·5	21
					13–24	„	25	1·60	0·085	81	20
4	M	40	R.A.	1	Control	—	—	1·60	(11)ª	67	24
					1–9	Corticotrophin	29	1·77•	0·06	71	25
					10–18	„	29	1·69•	0·08	71	24
5	M	50	R.A.	17	Control	—	—	1·32	(22)ª	59	22·5
					1–12	Corticotrophin	24	1·34	0·07	66	20
					13–24	„	33	1·33	0·09	70	19
6	F	35	R.A.	6	Control	—	—	0·93	0·11	50·5	18·5
					1–10	Corticotrophin	33	1·00	0·035	54	18·5
					11–20	„	26	1·00	0·12	56	18
					21–30	„	26	1·07	0·12	57	19
7	F	68	R.A. + S.D.	6	Control	—	—	0·7ᵇ	—	50·5	14
					1–12	Corticotrophin	27	0·78	0·08	57	13·5
					13–24	„	39	0·78	0·10	61	13
					25–36	„	16	0·83	0·10	64	13
8	M	21	R.A.	4	Control	—	—	1·38ᵇ	—	47·5	29
					1–12	Corticotrophin	36	1·38	0·06	52	27
					13–24	„	28	1·48•	0·12	50	30
					25–32	„	21	1·44	0·13	49	29·5
					36	Prednisolone	12·5	1·40	(5)ª	52	27
9	M	42	R.A.	10	Control	—	—	1·32	(20)ª	65	20
					1–2	Corticotrophin	30	1·5•	(20)ª	71	21
					6–18	„	20	1·51	0·09	71·5	21
					19–30	„	27	1·62•	0·10	73	22
					31–42	„	24	1·59	0·04	71	22·5
					43–56	„	21	1·57	0·08	71·5	22
10	F	37	A.S.	12	Control	—	—	0·80	(30)ª	48	16·5
					1954	Corticotrophin	17·5	1·15•	0·01	56	20·5
					1955	„	26	1·17	0·02	76	15·5
					1956	„	25	1·18	0·24	77	15·5
					1957	„	23	1·11	0·03	80	14
11	M	16	R.A.	4/12	Control	—	—	1·05	0·05	47·5	22
					1954	Corticotrophin	24	1·31•	0·10	50	26
					1955	„	37	1·44•	0·08	52	27·5
					1956	„	33	1·4	0·06	54	26
					1957: 1–6	„	34	1·37	0·07	52·5	26
					1957: 7–12	Prednisolone	12·5	—	—	—	—
					Feb. '58	„	12·5	1·27•	(20)ª	50	25·5
12	M	47	R.A.	3	Control	—	—	1·56	0·11	62	25
					1954	Corticotrophin	26	1·77•	0·09	74	24
					1955	„	40	1·79	0·14	76	23·5
					1956	„	28	1·60•	0·09	71·5	22·5
					1957	„	27	1·33•	0·09	66	20
13	F	31	A.S.	10	Control	—	—	—	—	50	—
					May, 1952						
					1953	Corticotrophin	—	—	—	54·5	—
					1954	„	20	1·23	0·09	56	22
					1955	„	35	1·19	0·12	61	19·5
					1956	„	30	1·30•	0·06	66	19·5
					1957	„	22	1·22•	0·10	68	18
14	F	30	R.A.	13	Control	—	—	1·06	(35)ª	46	23
					1–2	Cortisone	50	—	—	—	—
					28	„	50	1·28•	(2)ª	54	23·5
15	F	49	R.A.	2	Control	—	—	0·68	(7)ª	43	16
					1–2	Corticotrophin	32	0·86•	(15)ª	46	18·5
					3–12	„	15	1·06•	0·13	56	19
					13–30	Cortisone	62·5	—	—	—	—
					31	„	„	1·05	0·05	58·5	18
					32–51	„	„	—	—	—	—
					52	„	„	0·87•	0·2	54	16
16	F	40	R.A.	6	Control	—	—	0·98	0·04	47	21
					1–5	Corticotrophin	18	1·05•	0·08	54·5	19
					6–16	Prednisolone	15	—	—	—	—
					17	„	„	1·16•	(10)ª	58	20
					18	„	„	1·15	(12)ª	60	19
17	F	32	R.A.	4	Control	—	—	0·82	0·11	57·5	14·5
					1–10	Cortisone	75	—	—	—	—
					11–36	Prednisolone	15	0·81	0·12	67	12
18	F	19	R.A. + P.A.N.	4	Control	—	—	0·67	(7)ª	45·5	14·5
					1	Corticotrophin	22	0·74•	(6)ª	52	14·0
					2	„	29	0·86•	0·06	54·5	16·0
					3	„	31	0·92	0·17	55·5	16·5
					6–18	Cortisone	100	—	—	—	—
					17	„	„	1·03•	(11)ª	69	15
					18	Prednisolone	20	1·15•	(10)ª	66	17·5
					19–48	„	17·5	—	—	—	—
					49	„	„	0·81•	(22)ª	58	14
19	F	41	R.A.	5	Control	—	—	0·92 & 0·93	—	58·5	16
					1–10	Corticotrophin	21	1·14	0·11	64	18
					11–20	Cortisone	75	—	—	—	—
					21–44	Prednisolone	15	—	—	—	—
					45	„	15	0·79•	0·06	54·5	14·5

R.A. = rheumatoid arthritis. S.D. = scleroderma. P.A.N. = polyarteritis nodosa.

• = Statistically significant difference between this mean and that immediately above.

† Amount administered orally in divided doses in the case of cortisone and prednisolone. In the case of corticotrophin, the amount refers to mean daily urinary excretion of 17-ketogenic steroids or 17-hydroxycorticosteroids; the amount of corticotrophin (in gelatin or other delaying menstruum) injected daily varied from 8 to 50 international units.

‡ When the number (n) of assays was less than 20 the standard deviation was multiplied by $\sqrt{\frac{n}{n-1}}$

§ Creatinine coefficient = mg. of creatinine excreted per kg. body-weight.

a = consecutive assays. *b* = single determination. *c* = two specimens known to be collected accurately.

TABLE II—SUMMARY OF SIGNIFICANT CHANGES IN CREATININE EXCRETION BETWEEN THE CONTROL AND FINAL PERIODS FOR 19 PATIENTS, RELATED TO TOTAL DURATION OF TREATMENT

Duration (yr.)	Overall change		
	Nil	Increase	Decrease
½–1	—	1	—
1–2	4	1	—
2–3	4	1	—
3–4	—	1	2
4–5	2	2	—
5–6	1	—	—
Total	11	6	2

will be associated with a more than twofold increase in the effective level of cortisol in the plasma.

The Patients

Of the 19 patients 7 were men with rheumatoid arthritis and 12 were women. Of the 12 women, 2 had ankylosing spondylitis and 10 rheumatoid arthritis; 1 of the women with rheumatoid arthritis had in addition polyarteritis nodosa and another scleroderma. The mean age of the whole group at the start of therapy was 38 (16–68) and the mean duration of the disease was 5½ years (4 months to 17 years). These patients were selected for corticosteroid therapy because of the severity of their disease. The criteria used for their selection are not relevant, but at this centre one in about thirty rheumatoid-arthritic patients sent to us for treatment has been so selected.

Results

Table I shows the findings for every patient for whom a sufficient number of creatinine estimations had been made to justify statistical analysis. The muscle mass of a rheumatoid arthritic depends partly on his or her physical ability. The physical ability of this group of patients at the end of the period of observation may be summarised as follows: (1) patients earning their living outside their homes, 7 (nos. 3, 4, 6, 8, 9, 11 and 14); (2) patients running their homes without serious disability, 7 (nos. 1, 2, 4, 7, 13, 15, and 16); (3) patients grossly restricted in mobility but able to dress and move about slowly unaided, 4 (nos. 5, 12, 17, and 19); (4) patients wholly dependent on others, 1 (no. 18). In table I the creatinine coefficients reflect the weight of muscle relative to the total body-weight. The table shows that of the 29 significant changes in creatinine excretion between one period and the next, 21 were increases and 8 decreases.

In table II the overall changes between the control and final periods are summarised. Of the 11 cases in which there was no change 6 had at some time shown a significant increase. Of the 2 which showed a decrease 1 had previously had a significant increase. Thus of the 19 no less than 13 had had an increase in muscle mass at some time during treatment and only 1 had had only a loss.

The circumstances of the cases in which there was a significant fall in creatinine excretion are as follows:

Case 4.—This man is well and doing a full day's work without disability. His creatinine excretion remains above the control level.

Case 11.—Two factors contributed to the fall in this young man's creatinine excretion: (1) a reduction of effective dosage during the last six months; and (2) anorexia due to disappointment in love which ended in his taking an overdose of barbiturates just before his last admission and the collection of twenty consecutive twenty-four-hour specimens (he is now enjoying life again, taking 8 mg. of triamcinolone daily).

Case 12.—This man, who has severe destructive rheumatoid arthritis, came into dispute with his employing authority and union. He lost his job and subsequently became depressed in mind and body, eating little and taking no exercise.

Case 13.—This patient is well and looks after home and children without any disability. The fall in creatinine coincides with a decrease in effective therapy.

Case 15.—A chronic gastric ulcer and much-reduced food intake persisted throughout the last eighteen months of this patient's treatment.

Case 18.—This patient, who has rheumatoid arthritis and polyarteritis nodosa, began therapy in an emaciated state. During the first two years she improved a great deal, but the therapy did not halt the rheumatoid process. The fall in creatinine in her case has been accompanied by progressive crippledom and frequent gastrointestinal disturbances.

Case 19.—The fall in creatinine output in this patient was accompanied by a progressive decline in physical ability and two long periods of depression attributed to worry over the drinking habits of her husband.

The changes in creatinine coefficients recorded in the last column of table I reflect increases and decreases in the fat stores of the patients. Fluid retention played a relatively small part in these changes. Cases 4, 8, 9, and 11 (all men) have large appetites but do not lay down fat stores even on large doses of corticosteroids.

Discussion

It seems reasonable to deduce from these findings that the long-continued administration of corticosteroid hormones, in the doses used in this study, to rheumatoid arthritic patients is likely to be accompanied by a gain in protein stores rather than a loss, provided that the patients eat normally and take enough exercise to prevent muscle involution from disuse.

The findings relate largely to corticotrophin therapy, but clinical experience suggests that the findings would not have been different had more patients on cortisone or prednisolone been available for this study.

It follows from this that the concurrent administration of protein-anabolic hormones is not justified as a routine.

Short-term balance studies may reveal protein loss during corticosteroid therapy at certain dose levels and protein gain during therapy with testosterone or some of its derivatives at certain dose levels, but it does not follow that such states will continue over long periods. Dunlop (1955) has stated that the protein-catabolic effects of corticosteroid therapy are balanced by increased food intake. The ill patient usually has an increased appetite when given corticosteroid therapy, but it has not been shown that his appetite remains long above his normal level. Many patients on corticosteroid therapy deliberately restrict their food intake to prevent excessive weight gain. It may be suggested that in patients given adrenal-stimulation therapy the protein stores increase because adrenal output of androgens as well as of cortisol increases. This might be so if the androgens are secreted in sufficient amount to give rise to signs of virilism. The adrenal stimulation used in the present study did not produce any signs of virilism.

Conclusions and Summary

Changes in the protein stores, in the form of muscle mass, of 19 patients treated for from six months to over four years with corticosteroids have been followed by the measurement of creatinine excretion in a large number of twenty-four-hour urine specimens.

The patients' muscle mass either increased or remained the same provided they did not suffer from a complication causing a low food intake or become so crippled as to lose muscle owing to disuse involution.

These findings relate to certain dose levels: in the case of corticotrophin such a dose as will maintain a daily excretion of 17-ketogenic steroids or 17-hydroxycorticosteroids of 20–30 mg.; in the case of cortisone and prednisolone 50–75 mg. and 10–15 mg. respectively, by mouth.

There is no justification for the statement that corticosteroid therapy is protein-catabolic and/or protein-anti-anabolic without qualification as to dosage and the circumstances of the recipient. Further, there is no justification for the routine prescription of protein-anabolic hormones during long-continued corticosteroid therapy.

The substance of this paper results from the combined labours of the physicians, laboratory staff, and nursing staff of this Centre.

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LEUKÆMOGENS *

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BIOPHYSICS is defined as the application of the laws of physics to biological phenomena. In recent years radiation has become so prominent in both lay and scientific thought that there has been a tendency to regard the laws of physics as meaning the laws of radiation. Especially has this been true in connection with leukæmia, since the production of this disease by radiation has received so much publicity that "radiation" and "leukæmia" have become very closely associated. Whilst in no way wishing to underestimate the importance of radiation, we feel that this publicity has perhaps caused other possible factors in the production of leukæmia to be overlooked.

We were led to this conclusion by our inability to exclude ankylosing spondylitis as a possible factor in the production of leukæmia in spondylitics who had been treated by irradiation (Abbatt and Lea 1956). We have therefore used a large series of cases of leukæmia to investigate other possible leukæmogenic factors which have from time to time been suggested, but for which, as far as we can ascertain, no firm supporting evidence relating to man has ever been provided.

Materials and Methods

We had previously collected a series of 679 cases of leukæmia, which had occurred in males in the Services, from the records of the Ministry of Pensions and National Insurance (Lea and Abbatt 1957). The limitations of this series are described in our previous paper. We noted the date and place of birth, date of onset of leukæmia, date of death or duration of disease, and also the following alleged leukæmogenic factors: irradiation, fractures, injuries other than fractures, sulpha drugs, antibiotics, chronic sepsis, acute infections, and the rheumatic diseases. These factors were recorded only when they clearly antedated any symptoms which could be referred to leukæmia. Finally we recorded the presence of other diseases which gave us a residual group of cases in which no previous history of disease or injury was recorded. The following conditions were included:

Irradiation.—Only therapeutic and occupational exposure to radiation have been recorded. It was hoped to record diagnostic radiation, but the probability of unnoted mass miniature radiography, both before and during service, was so great that this was abandoned.

Fractures.—All conditions in which the bone was penetrated—e.g., guttering for osteomyelitis, &c.

Other injuries.—All injuries to any part of the body, except fractures, sufficiently severe to require medical attention.

Sulpha drugs.—All the drugs of this group.

Antibiotics.—Penicillin, with only two exceptions.

Chronic sepsis.—Otitis media, osteomyelitis, multiple boils, &c.

Acute infections.—All (including appendicitis, &c.), with the exception of acute rheumatism.

Rheumatic diseases.—All the conditions at present classified under this heading with the exception of arthritis following trauma. The records of this factor have been made in two groups: (1) those in which there has been hospital investigation with positive findings; and (2) all cases, including those with only a history of the disease.

Other diseases and injuries.—All such conditions when they have been sufficiently severe to require medical attention.

All the above definitions and restrictions apply equally to the control series. These have been constructed from strictly random samples (prepared by using Fisher and Yates' (1949) tables of random numbers) of (1) all the cases, whether of disease or injury, for which pension was claimed from the Ministry of Pensions and National Insurance during the period Sept. 4, 1939, to Dec. 31, 1955; and (2) all neoplasms, with the exception of the reticuloses (assuming these to be neoplasms), for which pension was claimed during the same period. The first series consisted of 813 cases, the second of 554.

The leukæmia and control series were then divided in two ways: (1) by age of onset, into the groups 15–24, 25–34, and 35 years and over; and (2) by years of onset, from 1940 to 1955 inclusive. The reason for these two methods of subdivision are:

(1) For the factors, irradiation, fractures, other injuries, chronic sepsis, rheumatic diseases, and acute infections, it is obvious that the longer a man has lived before developing leukæmia or the control condition the more probable it is that he has encountered one or more of these factors, and therefore division into age-groups at onset is essential.

(2) In the case of sulpha drugs and penicillin, division into age-groups is not appropriate. These drugs have come into general use only since the beginning of the war, and the probability of having received them will therefore vary with, other things being equal, the year in which leukæmia or the control condition developed. Direct comparison of the incidence of these drugs in two groups of cases, one developing leukæmia in 1940 and the other in 1955, would clearly be absurd. For this reason the control and leukæmia series have been compared year by year for these factors.

We were forced to leave the question, "has leukæmia any relationship to ankylosing spondylitis itself?" in a state of uncertainty in a previous paper (Abbatt and Lea 1956). In an attempt to answer this question the Ministry's records of cases diagnosed as rheumatism and diseases of bones and joints from the 1914–18 war were searched for those cases which would now be diagnosed as ankylosing spondylitis. Some 12,500 case-records were examined, and it was hoped that, as most of these cases were not treated by irradiation, we would obtain

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TABLE I—INCIDENCE OF RHEUMATIC DISEASES (CASES TREATED BY IRRADIATION AND/OR SULPHA DRUGS EXCLUDED)

Age at onset	Series	All cases of rheumatic disease	Confirmed rheumatic disease	No rheumatic disease	Totals
15–24 years ..	Leukæmia	9 (*4·7*)	4 (*2·9*)	179	191
	Controls	10 (*2·1*)	1 (*0·2*)	464	474
25–34 years ..	Leukæmia	13 (*5·2*)	9 (*3·6*)	229	250
	Controls	16 (*3·3*)	5 (*1·0*)	474	490
35 years and over	Leukæmia	32 (*13·4*)	24 (*10·0*)	199	238
	Controls	25 (*6·0*)	14 (*3·4*)	389	414

Italic figures in parentheses are percentages of that age-group.
Comparison of all cases of rheumatic disease, leukæmia, and controls, gave the sum of the difference of proportions as $0{\cdot}1258 \pm 0{\cdot}0300$, 4·2 times the standard error. Comparison of the cases of confirmed rheumatic disease gave $0{\cdot}1045 \pm 0{\cdot}0245$, 4·3 times the standard error.

sufficient evidence to provide a firm answer to this question. A number of objections could be raised against this method, the obvious ones being uncertainty of diagnosis and the possibility that a number of early cases of the disease which did not progress would be missed, thus producing a selected series of severe cases only. It was our intention to overcome the first objection by submitting the evidence to an independent panel of experts, but, as will be seen later, this was not necessary.

Results

We obtained from the 1914–18 war records 201 cases which we considered to be ankylosing spondylitis. None of these had received treatment by irradiation and they were therefore added to our previous series of unirradiated cases of this disease. The combined series was then dealt with by the methods of cohort analysis, but it was found that the numbers were still too small to exclude the possibility that ankylosing spondylitis itself was a factor in the production of leukæmia. Because of this there was no point in attempting to deal with the objections which could be raised against the method used.

In the three series drawn from cases occurring during 1939–55 we eventually had to abandon the factor "acute infections" because of the nature of the evidence. In many cases the pre-service history was limited to an expression of the type "usual childish complaints", which was too vague for interpretation and could obviously range from a common cold to diphtheria.

Comparison of the two control series revealed no significant differences between them for any of the observed factors, and we were therefore able to combine these series for purposes of comparison with the cases of leukæmia. Comparison of the combined controls with the leukæmia series showed no significant differences in the incidence of any factors with the exception of irradiation, rheumatic diseases, and sulpha drugs. It will be obvious that there is considerable overlap between the incidence of these three factors. Radiation is known to be leukæmogenic, and a proportion of the cases with rheumatic diseases received radiotherapy. Similarly, a proportion received treatment by sulpha drugs for various infections. It follows that an association of leukæmia and the rheumatic diseases could be fictitious and due to the presence of one or both of the other two factors. All cases of the rheumatic diseases in which either or both of the other two factors were also present were therefore excluded from the leukæmia series, the results being shown in table I. It will be seen that in each age-group, both for all cases of rheumatic disease and for those with clinical and radiological confirmation, there is a large excess of cases of these diseases in the leukæmia series as compared with the controls. Comparison of this series with the combined controls showed that the difference was highly significant, and was only expected to occur by chance less than 1 in 1000 times.

TABLE II—INCIDENCE OF TREATMENT BY SULPHA DRUGS (CASES TREATED BY IRRADIATION AND/OR WITH HISTORY OF RHEUMATIC DISEASES EXCLUDED) (ACUTE LEUKÆMIA ONLY)

Year of onset	Acute leukæmia		Combined controls	
	With sulpha	Total cases	With sulpha	Total cases
1940	0 (*0·0*)	20	2 (*3·3*)	61
1941	1 (*2·6*)	39	5 (*4·9*)	102
1942	5 (*18·5*)	27	2 (*1·5*)	135
1943	3 (*5·7*)	53	8 (*4·8*)	168
1944	2 (*5·6*)	36	30 (*13·9*)	216
1945	8 (*16·3*)	49	22 (*10·9*)	202
1946	4 (*11·4*)	35	16 (*18·8*)	85
1947	6 (*23·1*)	26	12 (*21·1*)	57
1948	4 (*20·0*)	20	8 (*19·5*)	41
1949	5 (*31·3*)	16	7 (*25·0*)	28
1950	6 (*40·0*)	15	4 (*14·8*)	27
1951	2 (*25·0*)	8	10 (*18·5*)	54
1952	1 (*8·3*)	12	15 (*20·0*)	74
1953	7 (*50·0*)	14	8 (*11·9*)	67
1954	3 (*42·9*)	7	15 (*28·3*)	53
1955	7 (*53·8*)	13	8 (*17·4*)	46

Italic figures in parentheses are percentages of that year.
Comparison of this series with the combined control series gave the sum of the differences in proportion as $1{\cdot}1613 \pm 0{\cdot}4287$, 2·7 times the standard error.

In the same way those cases with rheumatic diseases and those treated by irradiation were removed from the series of cases receiving treatment by sulpha drugs (table II). Comparison of this series with the controls showed that the difference was again significant, and was only expected to occur by chance less than 1 in 100 times.

The number of cases treated by irradiation was too small for examination by this method. The irradiated cases are therefore given in full in table III. Comparison of the two control series showed no significant difference between them. Comparison of leukæmia and neoplasms also showed no significant difference. Comparison of the leukæmia cases with the series of all diseases and injuries showed a significant difference, the probability of it being due to chance being less than 1 in 100.

TABLE III—INCIDENCE OF IRRADIATION IN CASES OF LEUKÆMIA, ALL DISEASES AND INJURIES, AND NEOPLASMS OTHER THAN RETICULOSES

Age at onset (yr.)	Leukæmia		All diseases and injuries		Neoplasms other than reticuloses	
	Irradiated	Total cases	Irradiated	Total cases	Irradiated	Total cases
15–24	0 (*0·0*)	191	0 (*0·0*)	333	0 (*0·0*)	141
25–34	4 (*1·6*)	250	0 (*0·0*)	335	0 (*0·0*)	155
35+	6 (*2·5*)	238	0 (*0·0*)	156	3 (*1·2*)	258

Italic figures in parentheses are percentages of that age-group.
Comparison of the two control series showed no significant difference between them. Comparison of leukæmia and neoplasms also showed no significant difference. Comparison of leukæmia with the series of all diseases and injuries gave the sum of the differences in proportions as $0{\cdot}0412 \pm 0{\cdot}0141$, 2·9 times the standard error.

Validity of the Evidence

Before discussing our results we should like to deal with objections which can be raised against the material on which this investigation is based.

It has been suggested that when a person is seriously ill he will tend to remember or imagine illnesses and injuries more than will a healthy individual. This may be true, but in the series now reported, both leukæmia and controls, it is not a valid objection for either (1) events which happened before entry into the Forces, where we depend on the record of illness and injury made by the

TABLE IV—EXAMINATION OF THE 2×2 TABLES FOR EACH AGE-GROUP FOR ALL RHEUMATIC DISEASES AND CONFIRMED RHEUMATIC DISEASE (CASES TREATED BY SULPHA DRUGS AND/OR IRRADIATION BEING EXCLUDED)

Age-group (yr.)	All rheumatic diseases		Confirmed rheumatic disease	
	Difference in proportion	Diff./s.e.	Difference in proportion	Diff./s.e.
15–24	0·0267±0·0141	1·9	0·0188±0·0100	1·9
25–34	0·0210±0·0141	1·5	0·0241±0·0100	2·4
35+	0·0781±0·0224	3·5	0·0616±0·0200	3·1

recruiting board, or (2) for events which happened after entry into the Forces. With regard to (1) there is inevitable doubt as to what was disclosed by the man and recorded by the recruiting board, but there can be no grounds for suggesting that more details would be recorded in the case of a man who was eventually to develop leukæmia than in one who was eventually to develop some other condition. As far as (2) is concerned, after entry into the Forces, the nature of our evidence is such that all case-records are available.

It is to be expected that the incidence of the rheumatic diseases will increase with the length of time the patient has lived before the onset of leukæmia or the control condition. The percentages in table I show that this is true in every case, for both the leukæmia and control series. The same is true for the other factors investigated. Further, we have the records of cases in which no other conditions were recorded as being present, and these should obviously decrease in numbers with advancing age. This again is well shown in all series, the proportions of such cases in the combined series for the age-groups 15–24, 25–34, and 35 years and over being respectively 35·3%, 22·4%, and 17·8%.

It is well known that leukæmia often mimics the rheumatic diseases in its primary symptoms. Some of our cases were first investigated for lumbar pains, pains in various joints, &c., and were not infrequently treated for lumbago, or for subacute rheumatism. In some cases there was radiological evidence of joint involvement which, in the early stages, was diagnosed as rheumatic in origin. We cannot too strongly emphasise that all such cases have been excluded from the number of cases classified as having rheumatic disease before the onset of leukæmia. Our " confirmed " cases of rheumatism are those in which the confirmation of a rheumatic condition clearly antedated by years any symptom referable to leukæmia. Sulpha drugs are often used in the early stages of leukæmia for the treatment of gingivitis, pharyngitis, &c. Again we must emphasise that the histories have been examined with the greatest care, and that sulpha drugs have clearly antedated the onset of any signs or symptoms referable to leukæmia or to the control condition.

Although we have taken the greatest care to make sure that the presence of rheumatic disease antedated any symptoms or signs referable to leukæmia, the possibility remains of rheumatic symptoms themselves being the first and (at the time) only symptoms of leukæmia, and of these rheumatic symptoms antedating the more usual signs and symptoms of leukæmia by a number of years. In our present state of ignorance about the early stages of leukæmia we could not exclude this possibility. We can only say that in all our cases included under the heading " confirmed rheumatic disease " there had been hospital investigation resulting in a firm diagnosis of one of these diseases. However, when comparing the proportion of leukæmia cases encountering one of the rheumatic diseases with the proportion of the control series encountering one of the same group, it is to be expected that in the younger age-groups these proportions are liable to be the same (i.e., small) since in neither series have individuals had much opportunity of meeting the factor. On the other hand in the older age-groups the proportions will be expected to show differences increasing with age, because there has been a longer period in which to meet the factor. The data in each age-group for confirmed rheumatic disease were therefore examined separately and it was found that the expected effect was well shown (table IV, appendix). Such an effect would not be expected if the rheumatic diseases were in fact merely the pseudo-rheumatic onset of leukæmia. In those circumstances the differences between the leukæmia and control series would be expected to remain constant (within the limits of random variation). That this effect is so well shown strongly supports the view that the recorded instances of rheumatic disease in these series are in fact true cases, and not merely pseudo-rheumatic symptoms of leukæmia.

With sulpha drugs the statistical association was only with acute leukæmia, this being defined as a disease not exceeding six months. The differences between the two series would be expected to be greatest in those years in which the greatest number of cases had been treated with sulpha drugs. Detailed examination of the evidence showed that this was not so and that there were serious inconsistencies. We therefore regard the evidence on sulpha drugs as merely suggestive and by no means conclusive.

Discussion

Our results provide no evidence whatever in support of the suggestions that fractures, injuries other than fractures, antibiotics (penicillin), or chronic sepsis are related to the onset of leukæmia. On the other hand the results show that there is some form of association between leukæmia and (*a*) radiation and (*b*) the rheumatic diseases. Radiation is known to be leukæmogenic, and it would have been surprising if we had failed to find an association.

We have stated previously that we consider radiation to play a major part in the production of leukæmia in irradiated cases of ankylosing spondylitis. We still believe this to be true, but the present evidence indicates that the other rheumatic diseases are also associated with the incidence of leukæmia. This, in our view, precludes the use of such cases in radiation-induced leukæmia dose-response investigations.

The Medical Research Council's dose-response investigation into leukæmia and irradiation was based on the implied assumption that the death-rate from leukæmia amongst unirradiated cases of ankylosing spondylitis was not greater than that for members of the general population of the same age and sex (Court-Brown and Doll 1957). In this investigation our results (Abbatt and Lea 1956) were interpreted as supporting this assumption, and the statement was made that there was a significantly higher incidence of leukæmia in the irradiated group as compared with the unirradiated cases. It should be pointed out that we specifically stated (Abbatt and Lea 1956) that " the hypothesis that ankylosing spondylitis is a factor in the production of leukæmia cannot be excluded until a larger control series is available for comparison ", since we did not consider the observed difference to be significant. The results now reported demonstrate that the assumption that there is no association between leukæmia and unirradiated ankylosing spondylitis is not valid.

We have no new data relevant to the very vexed questions of the inter-relationships between the various conditions classed as reticuloses, nor the inter-relationships between the various conditions classed as rheumatic diseases. Yet, although there

is no agreement on details, it is generally accepted that there is some form of relationship within these two groups. It is, therefore, of interest to refer to a number of recent papers which suggest that there may be a relationship *between* these two ill-defined groups of diseases. These papers deal with the associated anæmia (Roy et al. 1955, Alexander et al. 1956); the evidence of associated bone-marrow defect (Richmond et al. 1956); extensive visceral involvement (Sinclair and Cruickshank 1956); involvement of the lymph-nodes (Motulsky et al. 1952); gout, leukæmia, and blood-uric-acid (Hickling 1958); and finally a general discussion of other systems (Short et al. 1957).

Short et al. found lymph-node involvement in about one third of their cases of rheumatoid arthritis and enlargement of the spleen in 6·5%. The difficulties of differentiating between rheumatic involvement of lymphoid tissue and that due to malignant lymphoma are particularly stressed by Motulsky et al. Davis et al. (1957) have stated that the association between multiple myeloma and rheumatoid arthritis is unlikely to be fortuitous in view of the number of such cases which have been reported.

Toxic factors have for long been postulated as a cause of leukæmia, notably benzene derivatives. Wilkinson (1951) stated that he had seen 10 cases of acute leukæmia which followed closely on treatment of other conditions by sulphonamides; he considered that the greatly increased use of these drugs might be one of the factors involved in the increased incidence of leukæmia. As the sulpha drugs contain the benzene ring an association between them and leukæmia would not be very surprising. Agranulocytosis and aplastic anæmia are known to follow the use of these compounds, and we have previously given reasons (Lea and Abbatt 1958) for suspecting that some of the cases so diagnosed are in reality cases of acute leukæmia in an aleukæmic phase.

In conclusion we should like to return to the question of the validity of our evidence and the uses which should be made of this investigation and others of the same type. The problem is the retrospective use of case-notes for research purposes. This was discussed by the medical section of the Royal Statistical Society on May 29, 1956. The conclusion reached was that, in spite of many doubts about their reliability, such records are invaluable for pilot surveys. It is in this light that we regard the results of the present investigation. Our evidence does show that there is some form of association between leukæmia on the one hand and rheumatic diseases and irradiation on the other, but it is not capable of determining the nature of these relationships. We believe that these are questions which can only be—and we hope will be—answered by other means.

Summary

A series of 679 cases of leukæmia has been obtained from the records of the Ministry of Pensions and National Insurance. Two control series, one of all diseases and injuries, the other of neoplasms other than the reticuloses, consisting of 813 and 554 cases respectively, have also been prepared from the same source. The incidence in these series of various factors alleged to be leukæmogenic has been compared.

Associations between leukæmia and (*a*) irradiation and (*b*) the rheumatic diseases have been found. The validity of the results derived from material used in this investigation has been discussed in some detail. The evidence does not permit of an explanation of these associations.

We are greatly indebted to Dr. C. A. B. Smith for the method of comparison used in this paper; to Dr. J. F. Loutit, Prof. W. V. Mayneord, Mr. D. Newman, and Dr. F. G. Spear for helpful advice and criticism; and to the chief medical officer of the Ministry of Pensions and National Insurance for permission to publish data taken from the records of the Ministry.

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Appendix

The method of comparison used was suggested by Dr. C. A. B. Smith and is derived from a consideration of the Fisher-Irwin-Yates exact treatment of 2×2 tables. For example, if, in any given year, the number of men developing leukæmia was n_a and of these x_a had been given sulpha compounds before the onset of leukæmia and y_a had not, and, similarly, in the same year n_b men developed the control condition, x_b having had sulpha compounds previously and y_b not, then a table can be constructed as follows:

	Sulpha drugs	*No sulpha drugs*	*Totals*
Leukæmia	x_a	y_a	n_a
Controls	x_b	y_b	n_b
Totals	X	Y	N

It can then be shown that the difference between the two series in the proportion of men receiving sulpha is $\frac{x_a}{n_a} - \frac{x_b}{n_b}$ with variance $\frac{XY}{(N-1)n_a n_b}$

This process is repeated for each year, and the differences in proportions summed, also the variances. The standard error of the sum of the differences is then given by the square root of the sum of the variances, so that finally we have sum of differences in proportion $= S\left(\frac{x_a}{n_a} - \frac{x_b}{n_b}\right) \pm \sqrt{S\left(\frac{XY}{(N-1)n_a n_b}\right)}$

PLATELET-AGGLUTINATING FACTOR IN GLANDULAR FEVER COMPLICATED BY JAUNDICE AND THROMBOCYTOPENIA

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A POTENTIALLY serious, though rare, complication of glandular fever is thrombocytopenia.

Gouchiron (1895) first reported epistaxis as a complication of this disease, and purpura was reported by McKinley (1923). Since then, many cases have been published, and the reports have been reviewed by Bernstein (1940) and Bethel et al. (1946). This complication has been described in about 1% of reported cases (Weschler et al. 1946, Read and Helwig 1945, Halcrow et al. 1943, Tidy 1934).

Recovery appears to take place in all cases. Cooley (1938) reported a fatality in a case he described as "lymphoid hyperplasia". Although this case is usually included in reviews of thrombocytopenia in glandular fever, his findings of 22% small lymphocytes and 8% large lymphocytes in the blood of the patient do not seem to justify a diagnosis in retrospect of glandular fever.

The reason for the development of thrombocytopenia is obscure.

The bone-marrow has usually been found to contain a "normal" or "increased" number of megakaryocytes (Kutzer and Allen 1950, Goldbloom and Denton 1948, Vaughan 1944, Lloyd 1944, Volpe et al. 1953). Read and Helwig (1945) reported 3 cases with hypoplasia of all cellular elements and concluded that this was responsible for the

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peripheral platelet deficiency. Ogilvie and Parry (1952) reported a megakaryocyte deficiency in 1 case. Angle and Alt (1950) considered hypersplenism to be the cause of the thrombocytopenia, as did Dameshek and Grassi (1946) who reported a case of clinical and hæmatological recovery after splenectomy; this patient had a history of a hæmorrhagic tendency over the previous two years. Bethel et al. (1946) considered that sulphonamide sensitivity may play a part. Lloyd (1944) suggested that the cause was a primary capillary lesion with accumulation of platelets at the purpuric sites.

In the case here reported, the presence of a circulating platelet-agglutinin was held to be responsible for the thrombocytopenia. The dramatic hæmatological response to cortisone is of interest.

Method

Platelets were collected from a normal group-O subject by bleeding through a large-bore needle directly into a siliconed tube containing acid citrate dextrose; the blood was then centrifuged at 1500 R.P.M. for ten minutes. The supernatant plasma was used as a normal platelet suspension.

Serial dilutions of the patient's serum and of a normal serum were made and mixed with equal volumes of the platelet suspension. These were incubated for an hour. An aliquot of each was then examined and the rest returned to the incubator for sixteen hours. The contents of each tube were examined under a cover-slip after placing a small drop on a microscope slide and searching the field with an oil-immersion lens. Siliconed glassware was used throughout these experiments; the platelets came into contact with an unsiliconed surface only in their short passage through a wide-bore transfusion-needle. The system for recording agglutination was as follows: + = occasional clumping; ++ = at least one clump per high-power field, but many free platelets; +++ = many clumps per field, some free platelets; ++++ = complete agglutination, no free platelets.

Case-record

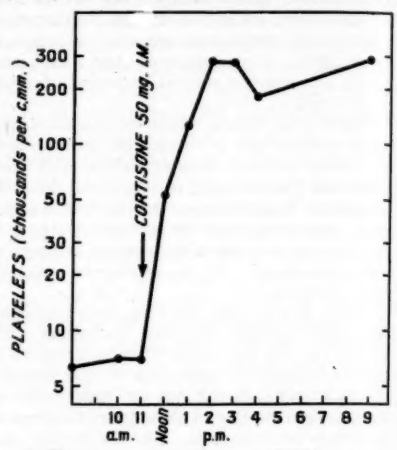
The patient, a soldier of 22, was admitted to hospital in 1955. For the previous week he had had mild anorexia and vague upper-abdominal discomfort. Over the previous twenty-four hours he had developed hæmorrhagic bullæ in his mouth and a purpuric rash on his trunk and limbs. He had five severe epistaxes on the day of admission. His urine on that day had been dark but not frankly bloodstained. He had no sore throat or joint pains. There was no history of contact with chemicals apart from a petroleum spirit (probably containing benzene) which he had used two weeks previously as a cleaning fluid for radio components. He had been taking no drugs. Apart from rubella, measles, and chickenpox he had never been ill before this episode. There was no family history of a blood disorder.

Examination

The patient was pale; his temperature was 101°F. Conjunctival icterus and subconjunctival hæmorrhages were present. There was a massive purpuric eruption on the limbs and trunk, and hæmorrhagic bullæ up to 2 cm. in diameter were present on the lips and oral mucous membrane. No enlarged lymph-glands were palpable. Pulse-rate 84; blood-pressure 140/90 mm. Hg. Tender liver edge was palpable 4 cm. below the right costal margin.

Investigations

Hæmoglobin 14·8 g. per 100 ml.; white blood-cells 9700 per c.mm. (polymorphs 5%, atypical mononuclears 27% [Downey types I, II, and III], monocytes 10%, lymphocytes 54% and eosinophils 4%); platelets clumped on the stained film, free platelets 500 per c.mm.; clotting-time 6 min.; bleeding-time over 25 min.; prothrombin-time normal. Paul-Bunnell test positive to a titre of 1:10,240; thymol turbidity 5 units; thymol flocculation 5+; total serum-proteins 5·4 g. per 100 ml. (albumin 3·0 g., globulin 2·4 g.); electrophoresis showed increase of α_1 and γ globulin. Urine was bloodstained, and the stools contained blood. Sternal marrow was normal; many normal megakaryocytes were seen.



Serial platelet-counts before and after a single intramuscular injection of cortisone 50 mg.

Platelet agglutination tests, by the method described, showed the presence in the serum of a factor that agglutinated normal group-O platelets to a titre of 1/5120, and this was unaffected by prior adsorption with guineapig kidney emulsion or ox red blood-cells (see accompanying table).

Progress and Further Investigations

The following day the patient complained of severe epigastric pain and passed a large melæna stool. He had further severe epistaxes and developed extensive bruising over sacrum, buttocks, and thighs. His hæmoglobin had fallen to 73% (packed-cell volume 32%), and his pulse-rate rose to 110–125, at which level it remained throughout the day. A pint of fresh blood (group-A, rhesus-positive) was transfused. His jaundice increased, and the cervical and axillary lymph-glands became enlarged. At 10 P.M. he passed a further melæna stool and vomited half a pint of altered blood. He was given a further 2 pints of fresh blood.

Next day his hæmoglobin was 72% and his clinical condition unchanged. No free platelets were seen in the peripheral blood. It was decided to administer cortisone. Platelet-counts were done hourly before and after 50 mg. of cortisone was given intramuscularly; the results of this are shown in the accompanying figure.

In view of the satisfactory hæmatological response, cortisone was continued orally 50 mg. t.d.s. His condition rapidly improved. No further hæmorrhagic episodes were noted. The platelet-count remained high and the hæmoglobin rose. The jaundice cleared slowly; excess urobilinogen was absent from his urine fourteen days after admission, and the liver became impalpable two days later. The cortisone dosage was diminished and stopped after eighteen days, at which time he was allowed up. He remained well during convalescence. On discharge a month after admission he showed no abnormal physical signs. His hæmoglobin was 17 g. per 100 ml. No Downey cells were seen in the stained film; the platelet-count was 395,000 per c.mm. The platelet-agglutinating factor was found to be still present, but the titre (1/320) had fallen considerably.

RESULTS OF PLATELET-AGGLUTINATION TESTS

Dilution of test serum	Patient's serum		Patient's serum adsorbed with guineapig kidney	Patient's serum adsorbed with ox cells	Normal heterologous serum
	Examined 1 hr.	After overnight			
1/2	0	++	..	..	..
1/10	0	++	..	..	..
1/20	0	++	..	..	..
1/40	0	++	++	++	+
1/80	0	++	++	++	0
1/160	0	++++	++++	++++	0
1/320	0	++++	++++	++++	+
1/640	..	++++	++++	++++	0
1/1280	..	++++	++++	++++	0
1/2560	..	++++	+++	+++	0
1/5120	..	+++	+++	+++	0
1/10,240	..	0	0	0	0

Because this man was an industrial chemist, and handling benzene and benzene derivatives was essential to his civilian livelihood, an attempt was made to eliminate the remote possibility of benzene exposure being the cause of the thrombocytopenia. He was exposed to benzene by the inhalation of 2 ml. of the chemical, which was allowed to evaporate from his cupped hands. His platelet-count at hourly intervals showed no fall.

The original serum that gave a titre of 1/5120 when first tested was stored frozen for two years. At the end of this time a repeat of the original test was positive to a titre of 1/160.

At this time Dr. J. F. Ackroyd kindly performed the standard platelet-agglutination test on this original serum and found it positive to a titre of 1 in 64. Platelet agglutination occurred within an hour.

The patient, when seen two and a half years after his illness, was well and showed no abnormal physical signs. His white blood-cells numbered 9100 per c.mm., with a normal differential count. No platelet-agglutinating factor was demonstrable in his serum by the method described, using platelets from the same donor.

Summary

A man with glandular fever, who had a positive Paul-Bunnell test to a titre of 1/10,240 and typical glandular-fever cells in the peripheral blood, showed impaired liver function and thrombocypopenia.

The thrombocytopenia was thought to be due to a factor in the blood that agglutinated group-O platelets to a high titre. This factor was shown not to be the same as the heterophil antibody, but no further evidence as to its nature was found.

The disorder responded dramatically to cortisone therapy.

After two and a half years the platelet-agglutinating factor was not present in the patient's serum.

We wish to thank Colonel W. R. Spicer for permission to publish; Dr. S. Epstein for managing the fresh-blood transfusions; and Dr. J. F. Ackroyd for confirming the presence of the platelet-agglutinin.

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Preliminary Communications

USE OF NILEVAR (17-ETHYL-19-NORTESTOSTERONE) TO SUPPRESS PROTEIN CATABOLISM IN ACUTE RENAL FAILURE

IN acute renal failure * the survival of the patient depends largely on whether he can be tided over the period of uræmia. Uræmia resulting from renal failure is usually assumed to be due to retention of metabolic breakdown products—probably mostly protein-breakdown products. Theoretically simple fats and carbohydrates are metabolised completely to CO_2 and water, whereas protein substances release not only urea and nitrogenous substances but also potassium and fixed acids, both of which are known to contribute to the toxicity of uræmia.

The basic principles in the treatment of a patient with acute renal failure are to avoid the intake of electrolytes and excessive water, and to reduce protein metabolism to a minimum. But in such patients the minimum protein breakdown that can be achieved with a glucose-and-water regime is still considerable, and often well above the level found in healthy subjects on the same regime.

Testosterone is known to produce a positive nitrogen balance when given to healthy subjects on a normal protein intake. Testosterone has in fact been administered in acute renal failure; but its precise value has not been established, and it is not widely used in this country.

We have recently made a study of the value of the synthetic steroid 'Nilevar' (norethandrolone, 17-ethyl-19-nortestosterone) in acute renal failure.

CASE-MATERIAL

The subjects of the study were 6 patients who developed acute renal failure following complications of pregnancy; 5 patients who developed acute renal failure from other causes; and 5 healthy subjects. The diagnoses are shown in the accompanying table. The patients were all referred to the General Infirmary at Leeds for treatment with the artificial kidney and had been treated with a protein-free regime for several days before transfer. The healthy subjects were volunteers.

* This term is preferred to alternative phrases—tubular necrosis, lower nephron nephrosis, &c.

CASE MANAGEMENT

All the patients were given the standard regime used for acute renal failure in this unit. This consists basically of 100 g. glucose and added vitamins in 400 ml. water daily by mouth. Additional water intake is calculated from the actual weight loss observed, so that the desired rate of weight loss 300–400 g. daily is achieved. Of the 5 healthy subjects 4 were given a standard constant diet of 600 calories containing only 2·0 g. nitrogen and 120 g. carbohydrate, and 1 (A) received the same glucose-and-water regime as the patients. 2 healthy subjects (A and B) remained in the ward more or less at rest during the study, whereas the other 3 carried on normal classes and duties as medical students throughout.

The patients and healthy subjects in this study were housed in the metabolic ward to ensure complete collections of urine.

EXPERIMENTAL METHOD

Urea production was used as the index of protein catabolism. The amount of urea produced per day was determined by adding together: (1) the daily excretion of urea in the urine, if any; and (2) the daily accumulation of urea in the body-fluids. The latter quantity was estimated by multiplying the daily increase in blood-urea levels by a figure for total body-

DATA ON 11 PATIENTS AND 5 HEALTHY SUBJECTS

Group	Case no.	Age (yr.)	Sex	Diagnosis	Mean daily urea production (g. N_2)	
					Control	Nilevar treatment
Acute renal failure: Obstetric causes	1	27	F	Abortion	9·1	1·8
	2	21	F	Accidental hæmorrhage	6·4	2·1
	3	27	F	Abortion; hysterectomy	4·1	0·2
	4	27	F	Glomerular disease	8·4	4·1
	5	39	F	Accidental hæmorrhage	6·6	2·3
	6	30	F	Placenta prævia; hysterectomy	4·3	1·9
Non-obstetric causes	7	50	F	Glomerular disease	6·6	4·8
	8	57	M	Ureteric obstruction	4·2	3·5
	9	33	M	Diodone reaction	5·0	3·0
	10	52	M	Glomerular disease	3·8	4·5
	11	24	M	Extensive burns	16·1	16·4
Healthy subjects	A	23	F		1·1	0·6
	B	31	F		1·9	2·1
	C	23	M		4·2	3·4
	D	23	M		3·9	3·3
	E	25	M		4·1	4·1

water based on the patient's weight. The body-water figure is an approximation, but any error will be constant for a particular patient and will not affect the results significantly.

Each patient acted as his own control, the first four days being used for this purpose and the subsequent five days being used to assess the effect of nilevar. (In our experience the daily rise in blood-urea remains fairly constant in acute renal failure until renal function returns.)

On the treatment days, nilevar 80 mg. daily by mouth in divided doses was given. 1 patient (case 2) received 100 mg. nilevar daily by intramuscular injection instead of 80 mg. by mouth. The healthy subjects had a period of equilibration on the low protein intake for five days before the control period started. 2 of the healthy subjects had control periods following and preceding the nilevar treatment period.

RESULTS

The results are shown in the table. The figures given represent the urea production per day expressed as grammes of nitrogen, the mean figures for the control period being compared with the nilevar treatment period.

There was distinct suppression of urea production in the obstetric group of patients when treated with nilevar, and relatively little effect in the non-obstetric patients or in healthy subjects on a very low protein diet.

COMMENT

It is reasonable to conclude that nilevar dramatically reduces the rate of protein catabolism in obstetric patients with acute renal failure—a group which accounts for 40% of the patients with acute renal failure referred to this unit. Further study is required to find out the relative efficacy of similar steroids, and why there is a different response in the various groups of patients.

The reduction of protein catabolism in the obstetric patients with acute renal failure in this study averaged 70%, and, if this can be maintained from the onset of renal failure by prompt administration of nilevar, it might largely eliminate the need for dialysis in the management of this group of patients.

Nilevar has anabolic and progestational effects, but it is interesting that the 2 obstetric patients who had undergone hysterectomy responded in the same way as the others.

We wish to thank Messrs. G. D. Searle & Co. for a generous supply of 'Nilevar'.

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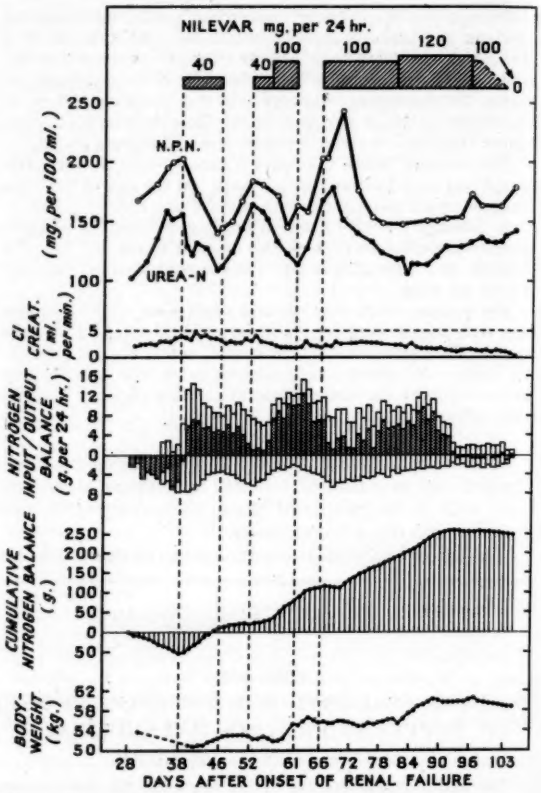

Observations during treatment of uræmia with anabolic steroid.

The patient was a 50-year-old woman with severe renal failure; the 24-hour endogenous creatinine clearance remained below 5 ml. per minute.

On the balance chart the intake of nitrogen per 24 hours is plotted upwards and the output downwards from the baseline; the daily external nitrogen balance is calculated as the difference between intake and output and indicated by hatched columns, upwards from baseline if positive and downwards if negative. The cumulative nitrogen balance is calculated from the external balance and corrected for changes in urea-nitrogen in the body-fluids.

For experimental reasons nilevar was chosen in this study, since the short-lasting effect of this compound makes possible a sharp delineation between treatment and control periods.

ANABOLIC STEROIDS IN TREATMENT OF URÆMIA

CLINICALLY useful anabolic substances have hitherto not been available for the treatment of uræmia. Testosterone and its derivatives have been found to be of limited value, and untoward endocrine reactions have restricted their application, at least over longer periods.[1]

Recently certain synthetic 19-nor-steroids—17-α-aethyl-19-nortestosterone (norethandrolone, 'Nilevar') and 19-nor-testosterone-17-β-phenyl-propionate (nondrolone, 'Durabolin') have been introduced as powerful anabolic substances with minimal side reactions.

The accompanying figure illustrates the effect of one of these substances (nilevar) on a patient with severe subacute renal failure. In the pretreatment period uræmia rapidly progressed despite minimal protein intake. In the treatment periods the levels of nitrogenous waste products in the serum decreased, despite high protein intake, causing considerable retention of lean tissue and gain in body-weight.

The compounds have been tested in 10 cases of severe chronic renal failure. In all, increased appetite, retention of lean tissue, gain in body-weight, and improvement of the clinical condition were observed. In no case did the increased protein intake cause an increase in biochemical uræmia, and it was surprising that the most common immediate reaction to therapy was a decrease in blood urea-nitrogen and non-protein-nitrogen similar to that illustrated in the figure.

Nilevar was given orally in doses of 50–100 mg. per 24 hr.; and durabolin was applied intramuscularly, generally in doses of 50 mg. per week. The effect of intramuscular durabolin was considerably longer than that of nilevar. With both drugs virilising side-effects were either not observed or minimal. In our hands nilevar had a definite progestative action, causing severe and long-continued withdrawal bleeding in 1 case.

1. Freedman, P., Spencer, A. G. *Clin. Sci.* 1957, **16**, 11.

From our preliminary observations we conclude that these 19-nor-steroids may break the vicious circle of progressive uræmic intoxication and approaching cachexia in patients with severe chronic renal failure. The ultimate prognosis naturally depends upon the possibilities for improving the underlying renal disorder. The clinical improvement brought about by the 19-nor-steroid treatment may, however, enhance the chances of adequate surgical or medical therapy of the renal disease.

The 19-nor-steroids have also been tested in the treatment of acute renal failure, in which condition they may retard the progression of biochemical uræmia. We consider, however, that the use of 19-nor-steroids in acute renal failure should be restricted to centres where supplementary hæmodialysis can be carried out whenever necessary.

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Reviews of Books

Aubrey's Brief Lives

Editor: OLIVER LAWSON DICK. London: Secker & Warburg. 1958. Pp. 341. 35*s*.

HISTORIANS and students of folk-lore have long been familiar with John Aubrey's name. For them, his nine surviving books have always been a Mecca wherein to search for information not to be found elsewhere. A rather different group of readers are all the amateur antiquarians who have at some time toured Aubrey's native county and, guide-book in hand, gazed at the enigmas of Stonehenge, Silbury Hill, and Avebury; for almost all the guide-books contain quotations from Aubrey's *Naturall Historie of Wiltshire*, and he wrote the earliest known description of the Avebury Circles. But the vivid writings of this indefatigable author (he tells us that, while still a boy, he studied even "on horseback and in the house of office") deserve to be more widely read. We hope Sir Geoffrey Keynes' Harveian Oration, which appears at the beginning of this issue, will enhance the popularity of this "charming and exasperating" character.

His most delightful work is probably the *Memories of Lives*, a collection of biographical sketches, jotted down over some twenty years but never properly prepared for the press until more than a hundred years after his death. Several editions of *Brief Lives*, as the book came to be called, have since appeared. But their style and price have often restricted their popularity. For many of the original 426 lives in the full collection are of no interest or are incomplete. (All that Aubrey has to say of one John Holywood, for instance, is "Dr. Pell is positive that his name was Holybushe"). The attractive edition prepared by Mr. Lawson Dick contains over 130 of the most important articles, well illustrated and prefaced by an admirable account of Aubrey's own life.

For the medical reader, Aubrey's most notable subject was William Harvey, whom he knew well in the physician's last years. ("I was at his Funerall, and helpt to carry him into the Vault"). But he also wrote of Willis, Hooke, and Descartes, to say nothing of a host of minor characters of medical interest who stray into his pages. (It is not difficult to diagnose the case of the licentious footman, whose "Nostrils were stuffed and borne out with corks in which were quills to breathe through"). Though it may be difficult to persuade a hospital library committee to invest in this volume, the season of book tokens approaches, and, while the committee hesitate, a doctor with a token in his hand may confidently surrender it for the new Aubrey.

De Circulatione Sanguinis

Two Anatomical Essays and Nine Letters by William Harvey. Translated by KENNETH J. FRANKLIN, D.M., F.R.S., professor of physiology, University of London. Oxford: Blackwell Scientific Publications. 1958. Pp. 184. 22*s*. 6*d*.

CANDIDATES for membership of the Royal College of Physicians of London were once required to show a certain competence in Greek or Latin by translating a short passage from one of these languages. That this did not tax all of them unduly is proved by the performance of one candidate (he was destined to become a regius professor of physic) who, doubtful of the examiner's intentions, handsomely rendered into Greek the Latin excerpt, and vice versa.

Since 1924 a knowledge of a classical language has not been an essential part of this particular qualification, and one consequence of the change may be that in years to come we shall be hard put to find a medical man sufficiently skilled to undertake such a work as Professor Franklin has now completed. The profession is already indebted to him for his masterly translation of *De Motu Cordis*, and that debt is now doubled. This translation comprises the original Latin text, and a new translation of William Harvey's two essays addressed to Jean Riolan, together with nine letters to various colleagues.

The Exercitationes of 1649 were written to refute Riolan's *Enchiridion*, a manual of anatomy which had appeared in the previous year, and in which the old Galenic fallacies about the circulation were repeated in an only slightly modified form. Till now these essays have seldom been read in the original text, and there has been a tendency to dismiss them as mere postscripts to the *De Motu Cordis*, published twenty years before. But, as Dr. Louis Chauvois has recently emphasised, they are important as showing how Harvey's first conception of the circulation was ripened and perfected by meditation and experiment over that interval. Apart from adducing new evidence to support his contentions, in these essays he makes the all-important point (not to be found in the 1628 treatise) that the heart itself does not in any way recharge the blood with "heat" or "vital spirits"

More than an expert ability in physiology and in Latin is evident in this book. Harvey lived in the golden hey-day of English literature, and his lectures and his writings must have reflected this fact before they were rendered into the international language. We may never know how these essays and letters read in their original draft. But, so deft and graceful is Professor Franklin's style, that it is easy to believe that they were not, in fact, dissimilar to the version he has now so handsomely provided.

Circulation

Proceedings of the Harvey Tercentenary Congress. Editor: JOHN MCMICHAEL, M.D., F.R.C.P., F.R.S., professor of medicine, University of London. Oxford: Blackwell Scientific Publications. 1958. Pp. 503. 50*s*.

THOSE who were unable to attend the very successful international congress held in London in June last year—and indeed those who did—will be gratified by the publication of the collected papers in an elegant small volume. The list of contributors gives promise of a store of knowledge in matters of the circulation, from its outset with the changes which occur at birth to the latest developments in cardiovascular surgery. There is much to interest every kind of reader: no-one, for instance, could fail to be pleased by an account by Weidmann of the study by direct capillary electrode of the intimate electrochemistry of the heart-beat, or to be astonished by Kety's revelation that cerebral blood-flow drops sharply at puberty, never to recover its earlier level. We might wonder whether after three hundred years this pure knowledge of function would interest William Harvey more than the miraculous achievements of heart and vessel surgery; or might he not perhaps, quite simply, being he, begin to look for the biggest unanswered question and start the great work anew.

Explorations in Social Psychiatry

Editors: ALEXANDER H. LEIGHTON, JOHN A. CLAUSEN, ROBERT N. WILSON. New York: Basic Books. London: Tavistock Publications. 1957. Pp. 452. 40s.

Social Class and Mental Illness

AUGUST B. HOLLINGSHEAD, PH.D., professor of sociology, Graduate School, Yale University; FREDRICK C. REDLICH, M.D., professor and chairman, department of psychiatry, School of Medicine, Yale University. New York: John Wiley. London: Chapman & Hall. 1958. Pp. 442. 60s.

OF these two interesting and important contributions to social medicine, *Explorations in Social Psychiatry* tends more towards the comprehensive, and in it a number of distinguished American workers contribute chapters of differing standard and interest, mainly reviews of relevant fields from a social standpoint, but with some accounts of new work. Tyhurst works out the concept of paranoid states and relates them to social forces, and Kubie argues from the universality of the neurotic process. Redlich reviews and criticises the literature on "the normal", and he suggests that progress will come by epidemiological survey of isolated features of illness—e.g., of compulsiveness, anxiety, or mood swing. The book then turns more to the particular and discusses neurotic family patterns, shared psychopathology, drugs and adolescence, bereavement, and the incidence of mental disease in different communities. Outstanding is Gruenberg's account of *folies à deux* and their wider implications.

As an example of the way medicine, sociology, and psychiatry are becoming fused in research, the work of Hinkle and Wolff is of especial interest. They took three groups of population, nearly 3000 people in all, and submitted them to a very careful physical, psychiatric, and social investigation. They showed that man's relation to his social environment had a great influence on his mental and physical health. Persons suffering more major and minor physical illness were usually the ones that also experienced some mental disturbance. Mental reactions might take the form of psychosis or neurosis, and the physical reactions usually affected more than one body system. Such illnesses tended to occur, not at random, but in "clusters" of five to ten years' duration which were related to some special difficulty in "adapting to the conflicting demands of the total environment". Hinkle and Wolff claim that heredity did not differ between the most healthy and the least healthy, but concede that constitution may have determined the forms of illnesses. They do not believe, however, that constitution could account for the "clustering".

Summaries are few, and all chapters have lengthy editorial introductions and discussions which do not fully succeed in relating one part of the book to another. Some of the discussions on sociopsychiatric subjects are too long and too vague, which is a pity because behind the word-screen there are many things of value.

Hollingshead and Redlich set themselves the challenging tasks of discovering, firstly, whether mental illness is related to social class, and, secondly, how far social class determines the treatment received.[1] As they have considered only patients treated by a recognised medical agency the first question is not fully answered: they say themselves that many people do not come for treatment, especially from the lower groups. Nevertheless the work they have reported and the facts they have marshalled make this one of the most valuable pieces of sociopsychiatric research: clearly set out, thoroughly documented, adequately summarised, it represents one of the best of the "interdisciplinary studies".

Psychiatric treatment depends to an alarming extent upon class position, and it is sad to learn that disturbed people in classes I and II are induced to seek help by "gentle and insightful means", whereas in classes IV and V the means are authoritative, compulsory, and even "coercively brutal". Class differences are especially important where the mentally ill infringe the law, and, though America may not be unique in these respects, the National Health Service is a powerful deterrent to discrimination of this kind. There is an inverse relationship between class position and mental illness, and class V especially contributes a much higher proportion of patients. Treated neurosis decreased lower in the social scale; but psychosis, especially alcoholic, organic, and senile, increased.

Anyone working in or around the field of social medicine or psychiatry should keep at his elbow this astringent though objective commentary on some of the ills of our time; and many others (including politicians) will find much to interest them. The forthcoming book from this project relating family dynamics to social class and mental illness will be eagerly awaited.

1. See annotation, *Lancet*, 1958, i, 952.

Principles of Research in Biology and Medicine

DWIGHT J. INGLE, B.S., M.S., PH.D., professor of physiology, Ben May Laboratory for Cancer Research, University of Chicago. New York and London: Pitman Medical Publishing Co. 1958. Pp. 123. 30s.

THE fallacies of many hypotheses formulated in the earlier years of "scientific" medicine have become apparent in recent years, and this realisation gives an opportunity to those with experience and responsibility to review some of the pitfalls in the path of the young research-worker. Professor Ingle's book is full of compressed wisdom, and all manner of laboratory difficulties are discussed. Statistical errors, personal bias, and suggestion are given first prominence, but other problems, such as the reactions of scientists to criticism of their favourite theories, and the problems of extra-laboratory distractions, will interest the more mature investigator. Freedom to dissent and debate are the very life-blood of science. Professor Ingle regrets that rising pressure on space for published data has set editorial policy against speculation, but "there is no theory without observational data and no experiment which is not motivated by an idea". Human error, human frailty, limitations of method, and the inevitability of sheer ignorance of yet undiscovered truths lead to a high mortality among our hypotheses.

Professor Ingle has indeed done the profession a service in this short but meaty monograph; his sage advice warns and yet comforts those who try to explore beyond the horizons of present knowledge.

Diseases of The Nervous System (9th ed. Edinburgh and London: E. & S. Livingstone. 1958. Pp. 373. 30s.).—There have been nine editions of this book since it was first published 18 years ago, and no other comment is needed on its popularity with the practitioners and students to whom it is addressed. It has grown in bulk with the years, but revision rather than addition has enabled Sir Francis Walshe to maintain an adequate and up-to-date presentation in less than 400 pages. One or two minor points may be criticised. The syndrome of episodic vascular insufficiency in the territory of the basilar artery is hardly discussed, though evidence is accumulating that this is as common as, or commoner than, the similar carotid syndrome. The long-continued use of anticoagulants in treating these conditions is certainly mentioned; but it is tucked away under the heading "treatment of hæmorrhage and softening". The use of hypotensive regimes gets little attention, though in the presence of hypertensive retinopathy many physicians would regard it as essential to give careful consideration to the use of the newer hypotensive agents. Corticoids in the treatment of post-exanthematous encephalitis are not mentioned: they are occasionally of striking benefit. In general, however, the book remains compendious and complete, and it will continue to be popular, not least because Sir Francis writes such clear English. In chapters on the neurological complications of liver disease and hepatolenticular degeneration, Dr. John Walshe gives a succinct account of a sometimes abstruse biochemical borderland of neurology. In a world where specialisation is tending to fragment knowledge, it is pleasant to find this book emphasising by precept and example the essential unity of medicine.

THE LANCET
LONDON 25 OCTOBER 1958

Carcinoma of the Cervix

ESTABLISHED cervical cancer is easily enough diagnosed provided the patient draws attention to her presenting symptom, which is nearly always irregular or postcoital bleeding, and provided the appropriate examinations are then made. Digital examination of the cervix is not enough; a speculum must be passed and the cervix examined in a good light. Rough areas must be probed for friability—a finding that is pathognomonic of carcinoma. Confirmation by biopsy is required in all cases. Difficulty arises when the cervix looks comparatively healthy; for how can one be sure that an early lesion is not being overlooked? Three widely differing techniques can be used to minimise this risk. The cervix can be painted with an iodine solution (1 part iodine and 2 parts potassium iodide to 300 parts of water); healthy tissue takes up the iodine as a brown stain and diseased tissues (not necessarily carcinomatous) will remain relatively uncoloured. This test shows where biopsy should be done, and it has the advantage of not requiring any special apparatus. By a second and more complex technique the cervix is scrutinised with a magnifying colposcope; this also directs attention to areas for biopsy. A newer test consists in examining the exfoliated cells that are lying either on the surface of the cervix or in the vaginal vault. This examination of vaginal smears has been extensively practised,[1] and in some parts of the U.S.A. it has become so much a routine matter that a gynæcologist might be judged negligent if he failed to undertake it. Here, by contrast, vaginal cytology has been tried only in a few of the larger centres.[2] The principal value of the vaginal-smear examination appears to be in detecting carcinoma-in-situ[3]; and this is borne out by a study, reported this week on p. 895, by the South-East Scotland Faculty of the College of General Practitioners.

In carcinoma-in-situ (intra-epithelial carcinoma, stage-0 carcinoma) there is lack of keratinisation, and the cells of the cervical epithelium look like carcinoma cells, but they have not yet broken through the basement membrane to become frankly invasive cancer. There is much controversy on this subject: the pathologists do not always agree as to what constitutes carcinoma-in-situ, and the clinicians do not know nearly enough about the natural history of the condition.[4] The majority view is that it is a precursor of invasive cancer; but cases have been followed for very many years before showing this change, and there is evidence that the process does not always go on to invasive cancer. Sometimes carcinoma-in-situ is found alongside frankly invasive cancer. For carcinoma-in-situ some believe that only local treatment—extensive conisation of the cervix or high amputation—is required. But others recommend total hysterectomy or a still more radical operation on the assumption that there may be areas of frankly invasive cancer alongside the non-invasive cancer. TELINDE,[5] who advises a wide hysterectomy, catheterises both ureters before operation so that these can readily be identified and the uterine artery ligated as far laterally as possible; he does not free the ureters from their beds in the surgical treatment of carcinoma-in-situ. An ample vaginal cuff is removed.

As regards the treatment of advanced cervical carcinoma there is not so very much difference of opinion. Nearly all gynæcologists and radiotherapists recommend radiotherapy, though a few prefer pelvic exenteration. With the early case, however, opinions are divided: some advocate radical operation, abdominal or vaginal; some maintain that radiotherapy is safer and quite as effective; some rely on a combination of radiotherapy and surgery, first shrinking and cleaning up the growth with radium or X rays and then performing the radical operation with removal of uterus, appendages, broad ligament, lymph-glands, and much of the vagina. CURRIE [6] has performed 214 radical operations over a period of twenty-one years, and records an 87% five-year-cure rate for stages 1 and 2a. Though he has used preoperative radium he is not at all convinced that this is necessary or desirable. He maintains that, if radium is to be used before operation, it should be inserted by the surgeon who is going later to operate: this advice has much to commend it provided the surgeon is guided by competent physicists and radiotherapists who can help to ensure that the correct dose is properly administered. A better solution would be for radium always to be applied, whether before operation or not, with both radiotherapist and gynæcologist present.[7]

Much work is being done on the radiosensitivity and the radioresistance of tumours. Among the most interesting studies is that of GRAHAM and GRAHAM,[8] who have studied the radiation response (R.R.) of the normal vaginal epithelium, by daily examination of smears. Four changes are described: "cytoplasmic vacuoles, increase in cell size, multiple nuclei, and an alteration in the nuclear appearance". These changes may be quantitatively measured, and it is claimed that a 70% or greater R.R. indicates a better prognosis than a smaller R.R. A five-year-cure rate of 65% is claimed for cases associated with a high R.R., compared with a 10% five-year-cure rate for those showing a low R.R. The GRAHAMS have also described a sensitisation response (S.R.) related to the finding before treatment of a densely finely vacuolated basophilic cytoplasm in the non-malignant basal cells of the vagina. When 10% or more of the cells show this characteristic appearance 70% of patients are alive and well after five years, compared with 15% of those showing less than a 10% S.R. KOTTMEIER [9] has reported similar figures: "a four-year-cure rate of 64% and 41% in good and poor S.R. cases".

Statistical comparisons between different methods of treatment abound, and many of these comparisons may

1. See Calabresi, P., Arnold, N. V., Stovall, W. D. *J. Amer. med. Ass.* 1958, 168, 243. Schulz, B., Carlson, D. J., Birge, E. A. *ibid.* p. 248.
2. See *Lancet*, 1957, i, 624. Anderson, A. F. *ibid.* p. 738. McLaren, H. C. *ibid.* p. 839. Wachtel, E. *ibid.* p. 840.
3. McLaren, H. C., Taylor, C. W., Attwood, M. E. *ibid.* 1958, i, 398.
4. Lawson, J. G. *J. Obstet. Gynaec., Brit. Emp.* 1957, **64**, 488.
5. Telinde, R. W. Surgical Treatment of Carcinoma of the Cervix; p. 130. New York, 1954.
6. Currie, D. *J. Obstet. Gynæc., Brit. Emp.* 1957, **64**, 871.
7. Blaikley, J. B., Lederman, M., Simmons, C. A. *Lancet*, 1957, ii, 1329.
8. Graham, R. M., Graham, J. B. Progress in Gynæcology; vol. 3, p. 114. New York, 1957.
9. Kottmeier, H. L. *Amer. J. Obstet. Gynec.* 1958, **76**, 243.

be found in the annual reports from Radiumhemmet, Stockholm. A great deal of work and world-wide cooperation has gone into preparing these reports; but the comparisons therein can only have a limited value, for there is the difficulty (some might even say the impossibility) of ever classifying cases of carcinoma of the cervix so that like is compared with like. This difficulty is common to all clinical research, but it may be especially acute in cervical cancer because inflammatory thickening in the parametrium can so often not be distinguished from neoplastic invasion. The latest annual report [10] suggests that the overall five-year-cure rate is just under 43%; but when this figure is subdivided according to the stage of the disease at which treatment was carried out a very different picture emerges. The apparent recovery-rate for stage-1 carcinoma is nearly 64%; for stage 2, 44%; for stage 3, 24%; and for stage 4, 7%.

It seems, therefore, that the greatest hope of improvement in the results of treating carcinoma of the cervix lies in seeing the patients when the disease is at an earlier stage. There are great differences of opinion as to how this is to be achieved. Some strongly recommend the routine examination of vaginal smears at regular intervals, and others advocate the establishment of cancer-detection clinics, together with widespread public education. Whichever method is chosen, its effective application will clearly cost a lot of money and require a great deal of effort.

Anabolic Steroids

TESTOSTERONE has long provided a way of checking protein catabolism, though its scope has, perhaps, not been explored as thoroughly as it might have been—partly owing to the limitations imposed on its use, particularly in women and children, by its virilising activity. The therapeutic applications of steroids capable of promoting protein anabolism—or opposing catabolism—are now being re-explored because synthetic agents with reduced androgenic activity have become available. In our columns this week Dr. GJØRUP and Dr. THAYSEN from Copenhagen and Dr. MCCRACKEN and Dr. PARSONS from Leeds report some preliminary results with norethandrolone in renal failure. Norethandrolone (17-α-ethyl-19-nortestosterone, 'Nilevar') is said to have the same anabolic potency as testosterone with only about $^1/_{16}$ of its androgenic activity. The object of using anabolic steroids in renal failure is to reduce protein catabolism and hence, by depressing the production of nitrogenous end-products, to prevent their accumulation, together with potassium, in the blood. In acute renal failure following complications of pregnancy MCCRACKEN and PARSONS were able to reduce the production of urea by as much as 70%. So distinct was the effect that they suggest that treatment with an anabolic hormone, in conjunction with a protein-free diet, may obviate the need for hæmodialysis in this threatening medical emergency. Patients with acute renal failure due to other causes showed a disappointing response, and, in common with a group of healthy individuals consuming a diet low in protein, evinced little or no change in urea production when given norethandrolone. GJØRUP and THAYSEN, however, in cases of subacute and chronic renal failure treated with norethandrolone or nandrolone (19-nortestosterone-17-β-phenyl propionate, 'Durabolin') achieved a reduction in the serum content of nitrogenous waste-products despite an increase in the amount of protein allowed in the diet. The combination of increased dietary protein and anabolic steroid led to a gain in weight due to an increase in lean tissue.

Earlier experience with testosterone in renal failures suggested that this treatment might be more valuable in acute than in chronic cases, for the effect of the hormone tended to wane after about two weeks.[1 2] After trying testosterone in chronic renal failure FREEDMAN and SPENCER [3] concluded that the beneficial effect was small but that the treatment was worth using in acute exacerbations of chronic uræmia as well as in recent acute cases. The temporary decrease of blood-urea which they detected could be attributed entirely to a positive cell balance of protein and potassium, and not to any change in urea-clearance; the serum-potassium level was unaffected, and FREEDMAN and SPENCER emphasised that hyperkalæmia is best treated with oral or rectal sodium-phase cation-exchange resin.

Nitrogen retention tends to "escape" as treatment with norethandrolone is prolonged, but in the urinary excretion of calcium no such effect is detectable. PRUNTY et al.[4] used the hormone in cases of osteoporosis induced by treatment with cortisone and prednisone, with good effect in two patients. On page 877 of this issue Dr. WEST discusses the effect of adrenal stimulation on the body stores of protein in patients with rheumatoid arthritis. Unless the diet was poor or muscle activity seriously restricted, a gain in protein stores occurred during long-continued treatment. WEST finds in these results no support for the routine administration of anabolic hormones during protracted corticosteroid therapy; and the use of anabolic steroids to avert osteoporosis, though not without theoretical justification, certainly lacks the support of any controlled investigation. It may, however, not be justifiable to equate muscle bulk with the protein content of bone matrix in all cases; for osteoporosis, though commoner in postmenopausal women, may develop in active young men with good muscles after protracted treatment with cortisone or Δ steroids.

The wider application of anabolic steroids to counter the protein-catabolic phase of acute illnesses, accidents, or major surgery obviously requires very careful appraisal by those who have the resources to meet the exacting requirements of metabolic investigations. While the indications for its use are being defined it is well to remember that treatment of a patient in hospital for one week with norethandrolone may cost £4 or more, and that testosterone can often provide an acceptable alternative.

10. Annual Report on the Results of Treatment in Carcinoma of the Uterus, Radiumhemmet, Stockholm. 60. Sweden. Vol. II.

1. Forbes, A. P. Conference on Metabolic Aspects of Convalescence; vol. 6, p. 147. New York, 1944.
2. Kochakian, C. D. *Amer. J. Physiol.* 1950, **160**, 53.
3. Freedman, P., Spencer, A. G. *Clin. Sci.* 1957, **16**, 11.
4. Prunty, F. T. G., Brooks, R. V., Clayton, B. E., McSwiney, R. R. *Proc. R. Soc. Med.* 1958, **51**, 557.

Juvenile Epilepsy

SOON after the 1939–45 war the World Health Organisation helped the university neuropsychiatric clinic in Vienna to set up a juvenile epilepsy department. W.H.O. offered to help to train a team of workers in the neurophysiological, psychological, and social aspects; and the Organisation then found that it had uncovered a neglected area of medical practice: knowledge about convulsive disorders in childhood was fragmentary, and the recent spectacular advances in neurophysiology had not resulted in any notable advance in the care of afflicted children. In the past decade much progress has been made. An international group was convened by W.H.O. in 1955 to study the problem from many aspects—physiological, pædiatric, psychiatric, genetic, and social.[1] Classification has always bedevilled the study of epilepsy, and, as POND has recently shown,[2] no fully rational classification is yet possible. The study group were clear, however, that "idiopathic epilepsy" had ceased to be a useful term, and that the so-called teething convulsions of infancy must be grouped with other forms of epilepsy on both genetic and electrophysiological grounds. Probably some time will pass before doctors drop these terms, because they appear to simplify complex problems. But grubbing out bad old words is an important part of the mental hygiene of science, just as the invention of a fine neologism often heralds a fresh rush of understanding. Both activities hurt minds replete with hard and sharp-edged concepts. But in medicine, as in poetry and politics, it is the right words at the right time that mark the effective mind.

Just as the study group enlarge the concept of epilepsy to cover the convulsions of childhood, so they seem to cut off many of the borderland phenomena. Migraine, Besnier's syndrome, the periodic syndrome, enuresis, temper tantrums, and explosive disorders of behaviour have all, at various times, been classified with the epilepsies. Such a grouping is shown to be clinically and heuristically valueless. The anonymous author of the group's report is equally stern with loose thinking about the "epileptic personality".

"The study of personality changes in epileptics forms an instructive example of a priori thinking falsifying observation. When epilepsy was an hereditary disease or constitution an epileptic disorder (*epileptische Wesenänderung*) was described. Later, when the possibility of the effects of brain damage and of social pressures was entertained, the entities of the brain-damaged child and of the neurotic reaction to disability were envisaged. Neither of these concepts adequately covers the facts and moreover they all have the danger of creating entities (*Krankheitenbilden*) where none exist."

The notion that epileptics segregate from the general population by distinct defects of character dies hard. The new film *People Apart*, made by the British Epilepsy Association, shows that *apartheid* for epileptics still draws its strength from just such a confusion. The facts seem to be that most children with epilepsy have normal personalities; some epileptic children have disorders of intelligence and personality, but these disorders form no single entity. Children with petit-mal epilepsy have been shown by POND and BIDWELL[3] to be shy, quiet, withdrawn, conforming, and passive; children with rhinencephalic epilepsy, on the other hand, show the hyperkinetic syndrome described by OUNSTED,[4] with brashness, noisy extraversion, overactivity, fearlessness, and aggressive outbursts.

Psychology and electrophysiology have advanced along rather separate roads in the past twenty years. If clinicians can clear the ground a little more, these disciplines might fruitfully unite in the study of epileptic disorders. Each fit (if we look at it as HUGHLINGS JACKSON looked) is a natural experiment which alters the most distinctively human thing about us—namely, our power consciously to attend to our environment. This change coincides with striking and recordable changes in the electroencephalogram, and often with brief subjective experiences which resemble a psychosis in miniature. The factors which precipitate the fits may be social, emotional, genetic, grossly anatomical, or biochemical. The seizure discharge itself is, in fact, the outcome of a host of forces which vary in importance from child to child and which vary in any given child from time to time. It is not surprising to find that the W.H.O. study group was a meeting-ground for workers from many different disciplines.

The W.H.O. report and the report of the Cohen Committee[5] agree in proposing new centres for the investigation and treatment of epilepsy. The evolution of such centres should be gradual, because their staffs will need to acquire a rather comprehensive knowledge of pædiatrics, neurology, psychiatry, genetics, and electrophysiology—a formidable list.

1. Juvenile Epilepsy. *Tech. Rep. Wld Hlth Org.* 1957, no. 130.
2. Pond, D. A. *in* Modern Trends in Pædiatrics (edited by A. Holzel and J. P. M. Tizard); chapter 12. London, 1958.

Annotations

STAPHYLOCOCCUS ALBUS SEPTICÆMIA

Staphylococcus aureus these days presents us with all too many problems, but at least we have few doubts about its pathogenicity. Even commensal strains living a symbiotic existence in the nasal mucosa of carriers do not seem to differ in pathogenicity, in tests on volunteers,[6] from strains derived from septic lesions. When we isolate this organism from a patient we know we have a pathogen, the cause of present mischief or the potential cause of future trouble.

The significance of *Staph. albus*, on the other hand, even when it is isolated in pure culture from a patient with clinical signs of infection, is most difficult to assess. Occasionally the question is simply resolved by a coagulase test. Some coagulase-forming staphylococci produce white colonies, and these strains are as pathogenic as other coagulase-positive staphylococci. An entire outbreak of surgical wound infection due to a staphylococcus of this kind has been reported.[7] Such strains probably arise as variants of normally pigmented coagulase-positive staphylococci and Barber[8] has shown that in the laboratory

3. Pond, D. A., Bidwell, B. *Brit. med. J.* 1954, ii, 1520.
4. Ounsted, C. *Lancet*, 1955, ii, 303.
5. Report of the Subcommittee on the Medical Care of Epileptics. H.M. Stationery Office, 1956.
6. Elek, S. D., Conen, P. E. *Brit. J. exp. Path.* 1957, **38**, 573.
7. McDonald, S., Timbury, M. C. *Lancet*, 1957, ii, 863.
8. Barber, M. *J. gen. Microbiol.* 1955, **13**, 338.

coagulase-positive *Staph. aureus* readily produce white-colony variants which remain stable through many bacterial generations.

These coagulase-positive white-colony staphylococci are infrequent. It is the true coagulase-negative *Staph. albus* that causes difficulty, because it is so common a contaminant and is of such uncertain pathogenicity. In blood-cultures in particular, it is almost always assumed to be a contaminant; but a report by Smith et al.[9] reminds us that it may sometimes be present in the blood-stream as a pathogen. These workers collected over 90 reported cases of *Staph. albus* septicæmia; and they describe 5 cases of their own seen during the past two years, 4 following mitral valvotomy and 1 apparently arising spontaneously. We have previously commented on *Staph. albus* infections after cardiac surgery,[10] and it seems that they are becoming commoner as more mitral valvotomies are being done. Apart from these cases associated with heart operations, Smith et al. state that *Staph. albus* septicæmia is seen most often as part of an endocarditis arising when this organism infects valves previously damaged by acute rheumatism. Clinically the disease closely resembles subacute bacterial endocarditis caused by *Streptococcus viridans*, and in fact about 1% of all cases of subacute bacterial endocarditis are due to *Staph. albus*. A few cases of *Staph. albus* septicæmia arise without endocardial involvement, and these are found almost exclusively in patients debilitated by severe disease, in women post partum, or in the newborn.

These, then, are the circumstances in which the isolation of *Staph. albus* from a blood-culture is of clinical significance. It is important to recognise them because this disease, which untreated has a mortality-rate as high as that of *Staph. aureus* septicæmia, can usually be cured if treatment is started early with an antibiotic to which the isolated organism has been found to be sensitive.

THE HISTORY OF RUBBER GLOVES

THERE is a romantic ring about the story of how Dr. William Stewart Halsted of Johns Hopkins Hospital came to devise rubber surgical gloves which keeps it fresh in the mind long after more momentous events have been forgotten. He himself described how " in the winter of 1889 and 1890 the nurse in charge of my operating room complained that the solutions of mercuric chloride produced a dermatitis of her arms and hands. As she was an unusually efficient woman, I gave the matter my consideration and one day in New York requested the Goodyear Rubber Company to make as an experiment two pair of thin rubber gloves with gauntlets ". The experiment was successful, and other members of the surgical team adopted the use of such gloves.

Recent research in the New York Academy of Medicine[11] has shown that over half a century earlier a young physician in New Jersey, Richard F. Cooke, was working in rubber gloves. Three years before that, an American chemist, Guthrie, had succeeded in preparing, from oil of turpentine, a solvent for rubber. Cooke found that such a solution, applied to the hands before performing dissections or examinations, formed " an insoluble pair of India rubber gloves—perfectly impenetrable to the most malignant virus ".

Neither Cooke nor Halsted, it will be noted, was primarily concerned with protecting the patient. One sought to protect the operator from infection, the other his assistants from dermatitis. That the use of gloves might also benefit the patient first occurred to a third person—Thomas Watson, physician to the Middlesex Hospital—who lectured as long ago as 1840 on the desirability of developing a pliant and expendable glove for use in obstetrics and gynæcology. " One such glove might well be sacrificed to the safety of the mother, in every labour." There is, however, no evidence that Watson had rubber gloves in mind, or that he developed his ideas further.

Though Halsted found his gloves pre-eminently suitable for operating, and though he quickly realised how much they simplified sterilisation of the surgeon's hands, they were only gradually adopted in other hospitals. The reports of Joseph Bloodgood, his assistant, who was the first man to operate consistently in rubber gloves, did much to spread the custom. But as late as 1911 we find an American surgeon, W. B. Carr, writing of the practice[12]: "It may seem a small matter, and in most operations perhaps it is, but in some cases I am sure this one thing is the determining factor of life or death for the patient. I believe firmly that more patients have died from the use of gloves than have ever been saved from infection by their use." Surgeons, it seems, are a conservative group.

DELIRIUM TREMENS

PROBABLY the first clinical account of delirium tremens was written of Demaenatus by Hippocrates, who noted acute fever, trembling of the head and particularly the lower lip, and eventually convulsions and complete delirium. Since then the disorder has not lacked attention[13]; but the diagnosis remains difficult. Many neurotics and some psychotics suppress their illnesses with alcohol, and when it is withdrawn acute mental symptoms may appear. Moreover, the end-stage of several addiction syndromes, including alcoholic addiction, consists in organic dementia; and this may be aggravated or induced by deficiency of vitamins, particularly those of the B group.[14] Alcoholism is commonly associated with cirrhosis of the liver, which may itself be associated with transient and reversible mental disturbances.[15] Clearly the appearance of acute mental derangement in a known alcoholic is not enough to justify the diagnosis: there must also be tremor, hallucinations, and severe restlessness culminating in delirium. To the practised eye the twitches, going on to the shakes, and ending in the horrors makes a characteristic enough picture.

Little is known of the pathogenesis of delirium tremens. It may develop during a drinking bout, or as a sequel to one, or on withdrawing alcohol. It is generally thought of as an effect either of chronic intoxication or of deficiency of vitamins.[12] The question of magnesium deficiency has been raised,[16 17] and this seems to warrant further investigation. The cause may finally prove to be multifactorial.

The effects of treatment are difficult to assess. Most of the patients are treated with sedatives, restraint, and a full diet, and usually the attack ends after a day or two by the patient falling into a deep sleep from which he awakens substantially recovered. Treatment with intramuscular magnesium sulphate has been recommended,[17] but is not usual in this country. The most widely used

9. Smith, I. M., Beals, P. O., Kingsbury, K. R., Hasenclever, H. F. *Arch. intern. Med.* 1958, **102**, 375.
10. *Lancet*, 1956, i, 273.
11. Proskauer, C. J. *Hist. Med.* 1958, **13**, 373.
12. Richardson, R. G. The Surgeon's Tale; p. 80. London, 1958.
13. See Wortis, H. *Quart. J. Stud. Alc.* 1940, **1**, 251.
14. Spies, T. *J. Amer. med. Ass.* 1940, **115**, 523.
15. Davidson, E., Soloman, P. *J. ment. Sci.* 1958, **104**, 326.
16. Flink, E. B., Stutzman, F. L., Anderson, A. R., Konig, T., Fraser, R. *J. Lab. clin. Med.* 1954, **43**, 169.
17. Flink, E. B. *J. Amer. med. Ass.* 1956, **160**, 1406.

drug is probably paraldehyde; but Figurelli [18] has recommended the administration of promazine (10- (3-dimethylaminopropyl)-phenothiazine) hydrochloride—a compound with pharmacological actions similar to those of chlorpromazine, though it is said to be less toxic. By its use Figurelli claims to have reduced the overall mortality for routinely admitted cases from 10 to 4·5%. This, if substantiated, is a notable advance; and the treatment is well worth further trial.

SOLAR LIPSTICK

THE cartoonist's picture of Manchester sitting under its private rain-cloud is resented by local patriots, but anyone who has approached Britain by aeroplane is aware how accurate this is for the country as a whole. Although we may deplore the cloud which prevents us from having a place in the sun, it spares us the cumulative effects of sunlight which cause keratoses and malignant disease of the skin. These are much commoner in Switzerland, for example, where the sun is strong, unfiltered by smoke or cloud, and reflected brilliantly by snow in winter as any pallid skier will testify. Our own stock, transported to Kenya or Australia, suffer prematurely from actinic damage and multiple precancers; basal and squamous cell carcinoma are common. The sunstroke myth and the sola topi have been so successfully debunked that we are in danger of allowing people to underestimate the harmful effects of excessive sunlight on European skins.

Where cutaneous sensitivity to light is acute, as in xeroderma pigmentosum and porphyria, patients welcome sun-screening applications and use them faithfully. The cream described by Smithers and Wood [19] is very effective symptomatically, and cases have been shown at meetings where the rate of premalignant and malignant change has been cut down by its use. But it is opaque, because it contains titanium dioxide, and men may hesitate to use it.

In Australia Mowatt and Robertson [20] have devised a form of protection for the lips of outdoor workers, to prevent atrophy, scarring, keratoses, and cancer of the lip. At the Queensland Radium Institute, 200 cases of frank cancer of the lip are treated annually. Ointments proved impracticable, as they came off and their renewal was inconvenient. Mowatt and Robertson found that a colourless lipstick was much more popular and, being convenient to carry, was used more regularly. They incorporated 5% salol, a known protective against light, and they showed it to be effective in the erythema range of the ultraviolet spectrum. They devised an ingenious apparatus to measure the effect on the transmission of light of several light-protective preparations in various thicknesses.

Incident light was suitably filtered to exclude the visible wavelengths. The light then passed through two plates of clear Corning glass 9700, which transmits wavelengths thought to be responsible for sunburn and skin cancer. Measured thicknesses of the preparations to be tested were placed between these glass sheets. The emergent light fell on to a layer of magnesium tungstate, which fluoresces when excited by the relevant wavelengths. This visible fluorescence was registered by a selenium photocell, the current produced being about proportional to the "erythemal effectiveness" of the incident light.

Mowatt and Robertson report that the condition of the lips in over a thousand cases was greatly improved by the use of the salol lipstick. If this is more than a subjective impression it must mean that not only are actinic effects preventable but that they are to some degree reversible. We hope that these workers will review their cases after some years and compare the number of cancers appearing in this group and in the unprotected population.

TREATING TUBERCULOSIS

TREATING pulmonary tuberculosis is no longer esoteric. No longer is it profitable to discuss the niceties of management of intrapleural pressures, the fine distinction between the lung too far down and the one too far up, the indications for blowing up the abdominal cavity, or the exact mechanism of the closure of cavities. These topics have, of course, given way to others—for instance, whether and when to excise parts of the lung; how long to continue prescribing drugs; and whether bacilli that can be seen but not grown are dead. But these have a foundation of morbid-anatomical, bacteriological, and clinical observations that belong to the common paths of medical knowledge. The principles of treatment now differ little, if at all, from those of any other infectious bacterial disease.

Judged by a recent report,[1] the treatment used at the Central Washington Tuberculosis Hospital seems to have been simplified and standardised so much that it can be summarised in a few sentences. Between 1952 and 1956 patients with all types of disease received streptomycin twice a week and *p*-aminosalicylic acid and isoniazid daily. No collapse therapy was used, and patients were allowed to go to the hospital cafeteria as soon as they were physically able to. Involved lung was resected if sputum cultures remained "positive" after three months or if the lesions were thought likely to reactivate, there being bronchial stenosis, tuberculous bronchitis, bronchiectasis, caseous masses 2 cm. or more in diameter, or persisting cavities. When discharged, all patients returned to their previous occupations, regardless of the physical activity involved.

It is claimed that this programme has reduced the mean duration of stay in hospital from 422 days in 1950–52 to 139 days in 1956; the cost per patient fell from 3270 dollars to 1641 dollars. 330 patients were admitted in the four and a half years. The group comprises patients with pulmonary and non-pulmonary tuberculosis, including a few (8) with meningitis. 33 died in hospital. All but 25 of the remaining 297 were followed up for at least two years. There was reactivation of the disease in 27. 153 returned to their previous light work, and 11 are known to have relapsed; 55 returned to moderately heavy work, and 5 relapsed; 89 went back to heavy work, and 11 relapsed.

All but 2 of the 330 patients eventually had negative cultures for tubercle bacilli with this regimen of drug and surgical treatment; 1 of these 2 had such extensive disease that resection was impossible, and the other had renal tuberculosis. 84% had negative cultures after four months' drug therapy.

Crofton [2] described the results obtained with chemotherapy and surgical treatment in 244 patients—all with pulmonary tuberculosis—in Edinburgh in 1952–56. 3 died with tubercle bacilli still present in the sputum. After four months 89% had negative cultures, and by the tenth month all surviving patients had negative cultures. Crofton used all three drugs in about a third of his cases, and daily streptomycin and isoniazid in another third. All patients had tubercle bacilli in the bronchial secretions

18. Figurelli, F. A. *ibid.* 1958, **166**, 747.
19. Smithers, D. W., Wood, J. H. *Lancet*, 1952, i, 945.
20. Mowatt, K. S., Robertson, D. F. *Med. J. Aust.* 1958, ii, 222.

1. Allan, A. R. *Amer. J. Med.* 1958, **25**, 75.
2. Crofton, J. *Amer. Rev. Tuberc.* 1958, **77**, 869.

before treatment, and the cultures were sensitive to at least two of the three main drugs. No drug-resistant bacilli were isolated at any time during or after chemotherapy with the regimens employed.

If the available drugs are wisely used and unproved combinations and modifications of them avoided, the treatment of tuberculosis is now highly effective, as well as far less mysterious than it used to be.

EARLY DIAGNOSIS OF CRETINISM

FOR many years cretinism has been the only disorder in which doctors have had the power to prevent permanent mental deficiency. Possibly other forms of mental deficiency—for instance, that due to phenylketonuria [1]—may turn out to be similarly preventable. If so, experience with the treatment of cretinism should prove a useful guide.

In cases of cretinism where treatment with thyroid extract seems to fail, it might be thought that the initial brain damage inflicted by hypothyroidism was irremediable by the time the doctor arrived on the scene. This comforting doctrine is not to be commended; and it would seem to be better to assume that when a cretin fails to reach intellectual normality some grave error has been made in diagnosis or treatment. Observation of treated cretins suggests that many of them remain at a subnormal intellectual level, and we understand that a systematic survey in the North of England is confirming this impression. Lowrey et al.,[2] of Ann Arbor, declare firmly that there is room for considerable improvement in the early diagnosis of cretinism.

The initial responsibility for suspecting that a child may be a cretin rests inevitably with the unaided clinician—the family doctor or those in charge of infant-welfare clinics. There is no laboratory test for hypothyroidism simple enough to be used as a screening-test. The first hint is likely to come from what the mother reports about the behaviour of her infant. In 50% of Lowrey's series of 49 cases, three or more of the cardinal symptoms were present during the first month of life. He and his colleagues lay particular stress on lethargy, constipation, feeding problems, and respiratory difficulties. Lethargy, even when present, may not be reported to the doctor, since the parents are likelier to welcome than to complain about the absence of crying. In a third of Lowrey's patients constipation was already recognisable by the end of the first month. Feeding difficulties seemed to be related to the infant's somnolence and lack of interest, and in some cases to the large tongue. Respiratory distress is not usually regarded as a symptom of cretinism, but was present (with cyanosis) in 15 of the 49 cases at some time in the first few months of life. In addition to these symptoms many mothers had noted the dry skin, large tongue, and umbilical hernia which feature in the classical descriptions of the disease.

In their account of what can be learnt from physical examination of the suspected cretin, Lowrey et al. lay less stress on the classical textbook findings (which may take many months to develop) than on simple measurement of the infant's linear growth. This is a more sensitive index of hypothyroidism than body-weight. All the cretins were shorter than would be expected from their age. A simple measurement of body length, in conjunction with standard normal tables, is probably the most practical screening-test for cretinism.

The laboratory investigations which Lowrey et al. found most helpful were serum protein-bound iodine (P.B.I.), radio-iodine uptake by the thyroid, and radiographic estimation of bone age. In all their cases in which P.B.I. was measured, the level was found to be below normal. It is a pity that this test, which is valuable for the diagnosis of hypothyroidism at all ages, is not more commonly used in this country. In infants (whose serum is unlikely to be contaminated by other iodine-containing compounds) the level of P.B.I. seems to give a true estimate of circulating thyroid hormone, except in the rare type of goitrous cretinism in which iodotyrosines contribute substantially to the protein-precipitable iodine of the serum.[3] The greatest objection to the use of radio-iodine tests in this context is the risk that the infant thyroid may be particularly susceptible to malignant change as the result of irradiation.[4 5] This objection can largely be overcome by the use of small doses (5 μC or less) of the short-lived isotope ^{132}I, instead of the more usual ^{131}I, in conjunction with sensitive counting equipment. The use of ^{132}I, however, limits observation of the proportion of the dose collected by the thyroid to a period of about six hours. Lowrey et al. found that the uptake was depressed at all time-intervals in all but 4 of their cases; and of these 4 patients, 3 had goitres.

Lowrey et al. did not find estimation of serum-cholesterol of much value, as the level was frequently normal in proven cases. Serum-cholesterol is probably relied on too greatly in this country, and opportunities of treating cretinism at an early stage may have been missed because the cholesterol level happened to be normal.

Lowrey et al. rightly condemn the administration of thyroid extract as a therapeutic test. The diagnosis of cretinism implies a therapeutic life-sentence and therefore should be established with the greatest possible certainty before treatment is begun. This need not conflict with speed of diagnosis if the machinery for investigation is well organised. Failure to adopt this principle will lead to some children being treated unnecessarily, and to interruption of the treatment of genuine cretins because of doubt about the original diagnosis.

Early diagnosis, and early initiation of treatment with thyroid extract, are not enough in themselves to ensure a cretin's normal development. This requires a sustained effort on the part of both doctor and parents to ensure that the dose of thyroid is optimal at all stages of growth. When the patient reaches adult life he must himself assume responsibility for the continuity of treatment. His success will depend on his mental development and his social circumstances. He will always be safer if someone—wife or relative—is at hand to ensure that the tablets are taken regularly. Adults with hypothyroidism (congenital or acquired) are in some danger, particularly when living alone, of falling into a vicious circle, with disastrous consequences. Treatment is neglected for a few weeks (perhaps the tablets are forgotten on holiday); hypothyroidism results, and leads to indifference or forgetfulness, and so to total omission of treatment. This is the story behind some of the fatal cases of myxœdema coma which have been reported.[6] Hypothyroidism should not be regarded lightly, as something which can be put right with a few tablets, but as a condition which needs great acumen for its initial diagnosis, and great perseverance for its successful treatment.

1. Bickel, H., Gerrard, J., Hickmans, E. M. *Lancet*, 1953, ii, 812.
2. Lowrey, G. H., Aster, R. H., Carr, E. A., Ramon, G., Beierwaltes, W. H., Spafford, N. R. *Amer. J. Dis. Child.* 1958, **96**, 131.
3. Stanbury, J. B., McGirr, E. M. *Amer. J. Med.* 1957, **22**, 712.
4. Duffy, B. J. *J. clin. Endocrin.* 1957, **17**, 1383.
5. Donisch, I. *Brit. med. Bull.* 1958, **14**, 181.
6. *Lancet*, 1956, ii, 768.

Special Articles

CYTOLOGICAL SCREENING OF 1000 WOMEN FOR CERVICAL CANCER

A Report by the South-East Scotland Faculty of the College of General Practitioners *

THIS report shows that the cytological detection of early cervical carcinoma can be undertaken in general practice. In this country until now cervical smears have been taken only from groups of hospital patients, from patients attending contraceptive clinics, and from gynæcological outpatients.

Papanicolaou and Traut's 1943 paper on exfoliative cytology demonstrated that cancer cells desquamate from a neoplasm of the cervix. During the past fifteen years or so it has become generally accepted that cervical cancer can be detected as an early preinvasive lesion in the squamous epithelium of the external os. (This pre-

TABLE I—ANALYSIS OF UNSUSPECTED POSITIVES ACCORDING TO THE INDICATION FOR TAKING THE SMEAR

Occasion for taking smear	No. of smears	Unsuspected positives
Postnatal examination	363	7 (*1·93%*)
Menopausal complaint	155	2 (*1·29%*)
Other reasons	482	6 (*1·24%*)
Total	1000	15 (*1·5%*)

invasive cancer is also known as intraepithelial cancer or carcinoma-in-situ.) It has been shown by Petersen (1956) that about a third of these lesions can develop into invasive cancers.

The average age in early cases detected by cytological examination is about 38, whilst the average age of presentation for all stages of clinically obvious cervical cancer is 48 years. It seems reasonable to assume that the ten years gained in diagnosis may be of considerable importance.

The Investigation

In 1955 Prof. R. J. Kellar invited the South-East Scotland faculty to take part in a research project on the early detection of cervical cancer. The general practitioners were instructed in the use of a wooden Ayre spatula and the fixing of slides. The slides were sent, with a note of the details of each case, to Professor Kellar's department.

The general practitioners taking part in this investigation took cervical smears during their ordinary consulting hours from three groups of patients:

(1) All women who came for postnatal examination.

(2) As many women as possible who had menopausal problems *without* histories pointing to any disease of the genital organs.

(3) As many women as possible in whom a complete medical examination was indicated for any reason other than gynæcological complaints, or women seeking advice on family planning.

* The following general practitioners took part in this investigation: I. A. D. ANDERSON, A. FRASER DARLING, B. C. HAMILTON, J. GOODBRAND, G. IRVINE, E. V. KUENSSBERG, LOWELL LAMONT, A. H. D. LARGE, A. R. LAURENCE, S. LIPETZ, D. MURRAY, R. MACGREGOR, D. MCVIE, D. W. MACLEAN, G. MACNAUGHTAN, M. W. MOSS, C. E. MUNRO, H. NEVE, M. PEARSON, A. D. ROBERTSON, R. SCOTT.

TABLE II—UNSUSPECTED POSITIVES CLASSIFIED BY AGE-GROUPS

Age (yr.)	No. of smears	Unsuspected positives
20 or under	9	—
21–25	160	—
26–30	228	2 (*0·88%*)
31–35	180	5 (*2·78%*)
36–40	123	4 (*3·25%*)
41–45	125	2 (*1·64%*)
46–50	98	—
51 or over	77	2 (*2·6%*)
Total	1000	15 (*1·5%*)

Results

Tables I-III summarise our findings. "Unsuspected positives" were patients who had a healthy cervix clinically (on inspection and palpation) but whose cervical smear was reported as suspicious or frankly malignant. The average age of "unsuspected positive" cases was 35·5 years; of the 7 patients who underwent hysterectomy 37 years; of patients who required amputation of the cervix 36 years; and of those still under surveillance after ring biopsy 32·2 years.

Table III does not show the time interval between the first suspicious smear and the final diagnosis and operation, and it does not give all the grounds on which the final decision to operate rested. In most cases several repeat smears and biopsy specimens were taken. In cases 1–4 the biopsy was in itself sufficient to eradicate the whole suspected area: subsequent cervical smears showed no abnormal cells. Similarly, in cases 5–8 amputation of cervix removed the cancer.

TABLE III—HISTOLOGICAL DIAGNOSIS AND SUBSEQUENT HISTORY OF UNSUSPECTED POSITIVES

Case no.	Age (yr.) of patient	Mode of confirmation of diagnosis	Histological diagnosis	Subsequent history
1	28	Ring biopsy	Preinvasive cancer	Still followed up. Subsequent smears negative
2	30	Ring biopsy	Preinvasive	Still followed up
3	33	Cone biopsy	Preinvasive cancer	Still followed up. Subsequent smears negative
4	38	Ring biopsy	Borderline invasive epithelium	Still followed up. Subsequent smears negative
5	32	Ring biopsy, followed by amputation of cervix	Preinvasive cancer	Still followed up. Subsequent smears negative
6	33	Ring biopsy, followed by amputation of cervix	Preinvasive cancer	Still followed up. Subsequent smears negative
7	38	Ring biopsy, followed by amputation of cervix	Preinvasive cancer	Still followed up. Subsequent smears negative
8	41	Ring biopsy, followed by amputation of cervix	Preinvasive cancer	Still followed up. Subsequent smears negative
9	28	Ring biopsy	Preinvasive cancer	Total hysterectomy
10	29	Ring biopsy	Early invasive cancer	Total hysterectomy
11	32	Ring biopsy	Early invasive cancer	Wertheim hysterectomy
12	36	Cone biopsy	Preinvasive cancer	Total hysterectomy
13	39	Cone biopsy	Preinvasive cancer	Total hysterectomy
14	42	Ring biopsy	Preinvasive cancer	Total hysterectomy
15	53	Ring biopsy	Early invasive cancer	Radium

The following case-history illustrates the routine procedure:

In January, 1956, at a postnatal examination a positive smear was obtained in case 9. This was repeated in hospital and on two subsequent occasions in 1956. However, the patient became pregnant during this period of observation and was allowed to continue with her pregnancy. Postnatal examination yielded a further positive smear and a hysterectomy was finally performed in December, 1957, and the diagnosis of invasive cervical cancer was thus confirmed.

Discussion

Early fears that the Ayre technique would take up too much time, or that it would be resented by the patients, proved groundless. The operation was easily performed after a little practice, and very few slides had to be repeated because they were technically unsatisfactory. The smear was not intended to take the place of gynæcological investigation by a specialist. When the history or physical examination was suspicious, the patient was referred to a gynæcologist even if the cervical smear was negative. Similarly, if the family doctor received a suspicious report on a smear taken from a clinically unsuspected cervix, he referred the patient for further investigation.

Before the general practitioners became accustomed to examining the cervix visually as well as manually they may have had some difficulty in deciding whether or not the cervix looked suspicious. However, in all the 15 cases diagnosed on cytological grounds alone the gynæcologist confirmed that there was nothing clinically abnormal.

Admittedly this series of 1000 cases is still small, but the finding of 15 clinically unsuspected positives and of another 5 atypical cases is worth noting. In British series of hospital or special-clinic patients the incidence has been about half as high (Royal College of Obstetricians and Gynæcologists 1955); and in field-surveys in Georgia, Tennessee, and at the special cancer-prevention clinic in New York the proportion of clinically unsuspected positives was even lower (Erickson et al. 1956, Scapier et el. 1952). An incidence of approximately 2% in women attending for postnatal examination in the present investigation suggests that routine screening of this group is especially desirable.

For several reasons the average age of women who have their babies at home is slightly greater than that of women who are admitted to hospital. This may have given prominence in this series to the age-group 30–40 which included most unsuspected positives; but this underlines rather than detracts from the need for greater vigilance.

It has been said that pregnancy changes in the cervical endothelium are often suspicious but that they regress spontaneously after parturition. All postnatal positive smears in this series were still positive three to six months after delivery. In none of our cases was there spontaneous regression, and treatment was eventually required in all but one. (The exception was case 1, who has now been followed up for two and a half years.)

In the minds of those who have taken part in this investigation there is no doubt whatever about the value of the smear as a routine screening-test: it should be part of every pelvic examination. It was particularly significant to find positive cases in the 30–40 age-group: this suggests a possible lag of ten to twelve years between the first positive smear and the appearance of a clinically detectable cervical carcinoma. Such a latent period has been demonstrated experimentally by Foulds (1951).

Summary

Cervical smears were taken from 1000 women. 15 unsuspected positives for early carcinoma were found—a higher incidence than in previous hospital studies.

To take such smears in general practice is simple and reliable. Cytological reports on such smears should be available to all general practitioners.

We are greatly indebted to Professor Kellar and his staff, in particular Dr. A. F. Anderson who examined the smears, in collaboration with Miss R. MacBryde and Miss K. Cockburn, for their constant advice and encouragement. We are also grateful for the helpful advice of Mr. S. A. Sklaroff, lecturer in the department of public health and social medicine, Edinburgh University. A grant was provided by the Scottish Advisory Committee on Medical Research.

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A HOSPITAL WORKSHOP *

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ALL the different types of sheltered hospital workshops so far established in this country have had to contend with two difficulties: first, they have been completely dependent on a continuous even supply of suitable material from outside industry, and secondly, they have found it hard to provide chronic psychotic patients with simple assembly work in sufficient variety. Our own industrial unit, started two years ago, has on the whole been successful and has raised many interesting points. For instance, though the patients were all doing the same work of assembling umbrellas, or should have been doing the same work (for they were all producing the same end-product), differences in practice crept in, though a standard method was taught originally. Such differences may appear slight and superficial, but when taken with tempo of work, they could easily account for almost all the variation in earnings between patients. On a straight piece-work basis, it is speed, used effectively, that governs the size of the pay-packet. The twin principles of financial payment and speed lift the work done by patients into the same category as work done by outside healthy workers—in distinction from traditional occupational therapy, which, by definition and association, is only done by those ill enough to remain in hospital.

SETTING NORMAL STANDARDS

The problem is, in part, one of communicating to the patients normal outside standards of tempo, which in the leisured setting of occupational therapy have little

* Abridged from paper to the Royal Medico-Psychological Association on April 30, 1958. The Nuffield Provincial Hospitals Trust have given a grant to cover research on this project.

significance. In occupational therapy time standards can be set only by the occupational therapist. Many of the tasks are relatively unstructured and the patients are encouraged to be original, and the time taken is relatively unimportant. Patients working on occupational-therapy tasks cannot be expected to communicate desirable standards of tempo to each other. On the other hand, it should be possible to introduce normal standards of work tempo into a hospital workshop if outside workers are brought in and work at a normal pace.

OUR SUGGESTIONS

The difficulties we met in running our industrial unit led us to consider further the whole problem of the type of work so far attempted in hospital workshops. As a result we have now decided to introduce two new principles:

That the hospital should develop its own industry.—A product should be both manufactured and marketed by the hospital so that the full profit should be available for the remuneration of patients and the support of scientific investigations into treatment connected with the workshop.

Employment of normal labour as well as patient labour.—This measure allows the workshop to become self-supporting. The nucleus of normal workers should enable the workshop to cope with the changing pressures of modern commerce, yet allow us to prescribe work to patients with the same freedom as a physician prescribes medicine. Patients may work in a protected environment while sharing the atmosphere of a normal workshop.

One tremendous advantage of a sheltered workshop will be that it offers scope for variety, instead of being confined, as in piece-work, to one or more simple techniques. The bigger a sheltered workshop becomes, the more variety of employment can be offered to patients.

Our decision to make Christmas novelties in the workshop was taken for the following reasons:

The materials used had to be cheap, so that if an article is damaged during manufacture the loss is small.

The work must not need a large capital outlay in machinery or plant.

We wanted something which could not be completely mechanised, so that there would be little danger of processes now undertaken by hand becoming automatic in a few years.

For our product we want the very quality avoided by outside industry—namely, variation in product design. We wish to undertake work which can be broken down into jobs needing a variety of levels of skill. This will meet the needs of our patients and give us opportunities for research into their ability to acquire these skills.

The problems of starting a business and research are small compared with the problems of conforming to Government rules and regulations. But we have been able to establish that mental patients, though working and earning "remuneration" (as opposed to "wages") in a sheltered workshop, are not in class 1 of National Insurance contributors, because there is no contract of service between them and the hospital. The hospital, therefore, does not have to pay an employer's stamp, and the patient may earn up to £2 per week without losing any sickness benefit. If he earns up to about £3 a week (in effect £3 12s., because the value of the stamp he would otherwise pay is deductible from the gross earnings) he may, if he has no other income, apply to a National Insurance office for exemption from the payment of a self-employed contribution.

The nucleus of normal workers will be kept to the minimum (and initially will be no more than the half-dozen required for running a research) provided the hospital as manufacturer designs its products to de-skill all tasks to make them suitable for the lowest common denominator among patients.

With later expansion the normal workers should not exceed, say, 20% of the total, especially if they are engaged only on any remaining skilled jobs, final inspection and packing, or as working supervisors, and as such they will earn their pay as in any outside factory where selling prices are fixed to take account of all forms of labour cost. From present experience and local response we do not believe it will be difficult to create incentives in a hospital workshop which will recruit and retain satisfactory normal workers.

RESEARCH

So much for the practical difficulties which we have so far met in starting a firm within a hospital. Later we hope to undertake research, but we cannot begin this on a long-term basis until the firm is producing and selling. We have, however, made a tentative beginning by employing a few patients during the preparations for industrial work.

To give one example, we found it convenient in our stock-piling of assemblies, to give an unstructured task to two patients. The task was the sorting of waste tangled elastic so that it could be cut into 15 in. lengths. The task was regarded as unstructured because the workers could only be given general and not detailed instructions. We observed that they were anxious about their progress, largely, we thought, because of the decisions they had to make. These decisions, whether to throw away a piece too short to be used or how to tackle some tangle, would be too petty to rank as decisions for the normal worker.

This sort of experience suggests that it may prove useful to structure jobs highly, as well as to destructure them for some classes of patient, even though the resulting tasks may well seem monotonous for normal workers. It is all too easy to project one's own feelings and dismiss industrial work out of hand as being too monotonous for patients. But it may well be that the continual low-level decisions needed in occupational-therapy craft work, are too demanding for some patients, and that it is at these points of decision that the patient withdraws and leans back in his chair to become absorbed in his own troubles instead of getting on with the job.

"... All shadow and mystery that lend enchantment to the play of children are being swept away. Modern dwellings are hygienic, practical, and well equipped. Every corner is utilized to the best advantage and the staircases are usually cold and dreary. There are no longer delicious dark attics under the rooftops; no cupboards under the stairs or unused corners either inside or outside the flat—no small niche where the child can be entirely by itself, where it can create its own world. ... The present light-fanaticism in architecture, the vast expanse of glass in home, and especially in schools, plays a part in the ever-growing nervousness of the present generation. This fashion of too much glare, too much daylight and neon lighting deprives the child of just what it seeks, and what it loves and needs. Shadows and twilight are as necessary to a child as sun and fresh air. The old-fashioned dark schools were in many ways much better suited to children than the modern school of steel, glass, and concrete, with large bare windows which leave no corner for the calming effect of half-light."—Lady ALLEN OF HURTWOOD at the annual meeting of the Housing Centre, as reported in *The Times*, Oct. 8.

The Widdicombe File

XLVIII. WHOSE PATIENT?

DEAR BREWER,

Your criticism of the management of Mrs. Smith's case is, I'm sure, quite justified. Indeed this isn't the first time you've suggested to me that there are too many people concerned in the care of some of your patients in hospital. I'm afraid there is a good deal of truth in what you say.

Mrs. Smith, I must confess, fell between two stools. In the outpatient department she was seen by a member of staff who has no beds in the hospital. In view of the history of irregular bleeding at the age of 48 and the presence of a lacerated patulous cervix, he advised hysterectomy. She was admitted to the ward, under my care, three weeks later. Examination under an anæsthetic in the operating-theatre revealed an endometrial polyp which, along with a cervical biopsy, was sent to the pathologist. After a favourable report had been received on the biopsy material she was allowed home. In my letter to you I suggested that we might keep her under surveillance for the next twelve months.

I can readily understand Mrs. Smith's bewilderment and must apologise for the failure to explain the situation more fully to her before she left the ward. To be told by one surgeon that she must have a major operation, and for this decision to be altered by another at the last moment, must make her wonder about the hospital's efficiency.

I know that it is common practice for regional consultants to have one or two outpatient sessions at the central hospital, but there are obvious disadvantages. It must be very frustrating to have to hand the patient over to the care of another consultant when inpatient treatment is required. For the patient, in these circumstances, there can be no continuity of care, and Mrs. Smith's recent experience shows what may happen.

In fact, I admit I'm worried about this question of who is really in charge of the patient. In the old days, when the surgeon, physician, or gynæcologist ruled supreme, there was no doubt in anyone's mind as to who was making the decisions; but with larger hospital staffs and more specialties there may now be doubt in the minds of doctors as well as patients.

I seem to meet this problem in some form every other week. Last month it arose over a blood-transfusion in the operating-theatre. While I was in the changing-room, after the operation, the registrar anæsthetist set up a blood-transfusion on the patient before she was taken back to the ward. Without my knowledge she received one pint of blood. I was more than surprised to learn about this when I was in the ward during the evening; the operation had been straightforward, with very little blood-loss, and at no time had the anæsthetist expressed concern about the patient's condition. As it happened, there was a reaction to the unmatched group O, Rh-negative blood, and she passed very little urine. The blood-urea rose steadily, and at one point we had some anxiety. Happily all went well in the end; but had there been any real trouble I wonder what would have been said. Was the responsibility mine?

As you know, our relationship with the radiotherapists in the hospital is particularly good, but I hear periodically from my colleagues in other centres about difficulties that crop up over the management of certain cases of malignant disease of the female genital tract. Is the patient to be treated by surgery, radiotherapy, or a combination of the two? If gynæcologist and radiotherapist disagree, who is really in charge of the patient? Who decides finally what is to be done? Who is immediately responsible for the continuing care and supervision of these important cases once the initial treatment has been completed? Perhaps most important of all—who is to decide what should be said to the patient and her husband? Does the husband come to the gynæcologist with all his fears, anxieties, and questions—or to the radiotherapist?

I know you'll have decided views about all this, and I'd like to hear them when next we meet. I recall that you had some very pertinent things to say about the confusion that arose over your Mrs. Brown in the Maternity Hospital last year. I've never really had the opportunity of giving you a full explanation.

Because she'd lost her first baby from pre-eclampsia about three years before, you referred her to me for hospital booking early in the second pregnancy. My hopes were high that all would be well, and I think that she and her husband shared my optimism. Her blood-pressure rose at the 30th week, and a few days later albumin appeared. The toxæmia slowly became worse until at the 33rd week the blood-pressure was 150/100 and the urine contained 2 g. albumin per litre. Unfortunately at this stage one of the registrars took it on himself to discuss the possible lines of treatment with her, and unwittingly gave the impression that unless a cæsarean section was done at once she might well lose the baby. When I spoke to her next day on the ward round she was quite agitated, and wanted to have an immediate cæsarean. I explained that the baby was very small and it would be wiser to wait a week or ten days before deciding upon delivery. I doubt whether she was able to follow my argument, and I sensed that she was losing confidence in me. As luck would have it, the fœtal heart sounds suddenly disappeared six days after the incident, and two days later she delivered a macerated fœtus weighing 3 lb. I need hardly remind you how disappointed I was. Mr. and Mrs. Brown said very little to me, but I can imagine what they thought.

I'm sorry to digress so far from Mrs. Smith; but her experience is but one example of a problem that is ever with us and must be faced. My colleagues and I are determined to put our own house in order, and within the department there is much that we can do to help. We are agreed that outpatient sessions should be linked with inpatient responsibility, and hope that in time the situation will be rectified. We have now made it a rule that when major lines of treatment are discussed with patients, this should be done by the consultant concerned rather than the registrar or houseman. We are going to make sure that, when a patient is discharged, the family doctor is fully informed about the facts so that he is in a position to explain them to the patient. I trust that in these ways things will improve and that you won't have further reasons for complaint.

But there may still be some awkward situations where two or even more departments are concerned in treatment. Nowadays the patient may be under the care of a small committee rather than an individual doctor. Such committees as I have served on have had a chairman, and I can see no alternative here. Someone must be in the chair; someone must have the final say. Who is it to be?

The intelligent answer is obvious, but much depends on the personalities of the various people. I need hardly tell

you that I think the gynæcologist should be the central coordinator. I don't know how physicians and surgeons tackle these situations: I must remember to ask them some time! In the meantime, I do want to assure you that we are increasingly aware of these problems of human relationships. I hope there will be less trouble in future.

With kind regards,
PETER GURNEY.

Medicine and the Law

Diminished Responsibility

IN Scotland the defence of diminished responsibility was known for many years before its introduction into English law in 1957, and it is instructive to turn to a recent Scottish trial in which the limitations of this defence were illustrated. This is reported in the *Scotsman* of Sept. 24, 25, and 26.

Donald Ferguson Forbes, a 23-year-old trawlerman, was charged with the capital murder of a night watchman aged 67. Forbes admitted to breaking into premises with intent to steal, and he also admitted that when unexpectedly faced by the watchman he killed and robbed him. It was contended on his behalf, however, that the charge should be reduced to manslaughter on the ground of provocation or, alternatively, of diminished responsibility.

Sir David Henderson described Forbes as "a psychopathic personality bordering on the insane". Having described the unhappy background of Forbes' youth, Sir David said: "His is one of those difficult conditions when one almost hesitates to differentiate between what one commonly calls sanity, and what one calls a certain state of mental instability which, from time to time, can be exaggerated by the circumstances in which the person is placed. . . . He is the nearest approach to what is called a 'psychopathic constitution' where reason and intelligence are unimpaired, but where a person, for the time being, is dominated by an episodic burst of conduct which is apt to come out in strained circumstances."

Cross-examined, Sir David said that Forbes was not suffering from any form of mental unsoundness which would justify his being certified and sent to a mental hospital.

Asked if Forbes were suffering from any form of mental disease, the witness replied: "A psychopathic personality is a person who is emotionally disturbed, and we cannot take a narrow view of what we mean by mental disease; mental disease is a huge thing. . . . This is a man who, in my opinion, corresponds to the psychopathic type of person who is essentially a law unto himself; almost the complete individualist." He would say that that was a sign of some form of mental disease.

Medical witnesses for the Crown who had examined Forbes in prison said that he was of sound mind.

Addressing the jury, the Solicitor-General for Scotland quoted the pronouncements of Scottish jurists in regard to the doctrine of diminished responsibility. It was demanded, he said, that to qualify for inclusion in this category there must be aberration or weakness of mind; that there must be some form of mental unsoundness; that there must be a state of mind bordering on, though not amounting to, insanity; that a person must be only partially accountable for his actions. It would not be sufficient to show merely that an accused person had a very short temper or was unstable or lacking in self-control.

Summing up, the judge said that in the present case no question of the accused being insane arose. But the question had sharply arisen as to whether or not the accused was suffering from diminished responsibility as the law recognised and interpreted that term. The defence must accept the onus of proving diminished responsibility, but this they could do on a simple balance of probabilities. His Lordship said that on this point experienced medical men had expressed conflicting opinions. "With such a subject as the human mind, it was perhaps not surprising that differences of opinion arose in certain cases." Forbes had had unfortunate and tragic experiences as a child. Whether the maladjustment from which he suffered as a child had subsided or proceeded into his present state, and whether that condition alone or in combination with other factors had produced a defect of mind sufficient to justify invocation of the doctrine of diminished responsibility, were some of the many aspects which the jury had to resolve.

His Lordship added: "I direct you in law that you are not entitled to hold diminished responsibility proved because you think there are mitigating circumstances in this young man's life, unless those circumstances constitute a condition of mind which in itself would justify the invocation of the doctrine of diminished responsibility."

The jury found Forbes guilty of capital murder, but added a recommendation to mercy. In the circumstances, the judge had no discretion as to sentence, and Forbes was sentenced to death. He has subsequently been reprieved.

In the final outcome a just and reasonable solution appears to have been found, but it has depended on administrative action rather than judicial process—the kind of situation which the Homicide Act was designed to avoid. The case therefore raises the question as to how far the Act can be regarded as satisfactory.

Appeal against Sentence for Abortion and Manslaughter

A doctor was convicted at the Central Criminal Court of unlawfully using an instrument to procure a miscarriage and manslaughter arising therefrom. He was sentenced to two years' imprisonment in respect of the first charge and three years' imprisonment on the second, the sentences to run consecutively.[1] At the trial the judge, in dealing with the manslaughter, left two questions to the jury—whether the manslaughter had resulted from the unlawful use of the instrument, or whether it had been occasioned by criminal negligence—and the jury specifically acquitted the doctor of criminal negligence other than by using the instrument. In sentencing, the judge said that in his view this was a very grave crime, and he added: "the day of reckoning has come for you, and you must have known what were the dangers to the lives of the women on whom you practised this, if there were others, and you must have known what would be the consequences to yourself if you were convicted." The doctor applied for leave to appeal against sentence on the ground that it was wrong in principle, in that separate and consecutive sentences had been given for what was really the same offence; and, further, that the judge had sentenced him on the basis that he was a professional abortioner, whereas the evidence disclosed no such suggestion. The Court gave leave to appeal and treated the hearing of the application as the hearing of the appeal.

The LORD CHIEF JUSTICE said that in the opinion of the Court the ground of appeal was valid. If the jury had found the doctor guilty of criminal negligence outside the use of the instrument there would have been grounds for consecutive sentences, but where, as here, it was in effect one offence—namely, the unlawful using of an instrument as a result of which death occurred—it was wrong in principle that there should be consecutive sentences. As to the second matter, the words used by the judge in passing sentence showed that he must have had in his mind the idea that the doctor was a professional abortionist. It was enough to say that there was abso-

1. See *Lancet*, 1958, i, 1134.

lutely no evidence whatever of that, and the doctor ought to have been dealt with on the basis that this was an isolated case. In the circumstances the Court would allow the appeal, and concurrent sentences of three years' and two years' imprisonment would be substituted for the consecutive terms.

REGINA *v.* NEWTON. *Court of Criminal Appeal:* Lord Parker *C. J.*, Cassels and Streatfeild *JJ.* October 13, 1958. Counsel and Solicitors: Harold Brown, Q.C., and Christmas Humphreys (Philip Conway Thomas & Co.)

E. M. WELLWOOD
Barrister-at-Law.

Public Health

Forward-scatter Radio Links

LAST week [1] *The Times* published prominently a report from its radio correspondent describing the hazards to health said to be involved in the operation of certain forward-scatter radio links to be set up in Britain under NATO arrangements. Each of these high-power two-way directional radio stations, it was stated, would have a "sterilised zone" in its beam extending a mile or so ahead of the station in the direction of the transmissions. "For their own safety the public will not be allowed permanently into those zones, and any occupied farms and homesteads will probably have to be evacuated". The development of more powerful equipment might make possible the generation of a radio "death ray".

Next day *The Times* published a statement from the Ministry of Defence saying that there was "a slight radiation hazard from the use of some new radio techniques". Precautions were taken at all sites where this risk might arise and a very small area, some 40 yards in depth in front of the cones, was fenced off. *The Times* commented that this statement apparently referred to existing stations and not to forward-scatter stations yet to be built. The medical aspects of radio-frequency radiation are being examined by the Medical Research Council, for whom the following points were made [2]:

"This hazard is nothing like nuclear radiation. This non-ionizing radiation does not produce the same biological changes, and is not thought to have any genetic effects on future generations.

"People who have been working with radar since the early days of the war have suffered no ill effects, and all the evidence of experiments on animals conducted here and in the United States goes to show that this type of radiation must be of a considerable potential to cause harm.

"In the sort of conditions in which people work at the present time in the radio industry we have no evidence there is any real danger."

Fallout on the Farm

The Agricultural Departments of England and Wales, Scotland, and Northern Ireland have prepared a handbook [3] to present in non-technical language information about radioactive fallout as it may affect the farmer and his work in the event of an attack on this country with nuclear weapons. In preparing the book the departments had the advice of a joint committee of the Agricultural Research Council, the Medical Research Council, and the Development Commission. It explains what might be the effects of radioactive fallout on farm animals and crops and what precautions can be taken to minimise these effects. The care of dairy cattle is given prominence because "the nation would need all the clean milk it could get". Contaminated milk could, it is said, be fed to pigs and steers because its radioactivity was unlikely to do them very much harm before they came to be slaughtered. On the subject of genetic damage to livestock the handbook says that "with heavily contaminated female stock some may become permanently sterile, others will remain fertile but with a chance that in some future generation, probably beyond our life-time, abnormal offspring may result".

1. *Times*, Oct. 14
2. *ibid.* Oct. 15.
3. Home Defence and the Farmer. H.M. Stationery Office. Pp. 32. 1*s.*

In England Now

A Running Commentary by Peripatetic Correspondents

MEDICINE is an art; and the art of "homonymo-diagnosis"—i.e., the diagnosing of a patient's disease by studying his christian name or surname—has received all too scant attention in a world medical press that in general places far too much emphasis on the scientific basis of medical practice. No-one would doubt that if a man called *Romanoff* walked into the outpatient department he would be suffering from hæmophilia, or if his name perchance was *Hapsburg* he would have macrocheilia. One asks, therefore, how far do such remarkable associations extend?

My attention was first focused on the value of homonymo-diagnosis some eight years ago when my Canadian registrar pointed out how dangerous it was for parents to call their baby girls *Doreen* or *Valerie*, for they would certainly develop bilateral bronchiectasis affecting the middle lobe of the right lung and the lower lobe of the left lung. Though this appeared to be a true observation, it was at that time reckoned to be an isolated one; but recent experience has shown that it obtains as much in the Southern as in the Northern hemisphere. Homonymo-diagnosis clearly has a far greater potential than has yet been appreciated in the philosophies of most physicians.

In this part of the world, to bear the name *June* is at once to raise the possibility of patent ductus arteriosus; and, as for being called *Lena*, one is at once assured that the patient is suffering from mitral stenosis, and, what is more, that she will get a good result by finger-fracture mitral valvotomy. Admittedly these coincidences may be regional, and other christian names may apply to other regions and diseases; but when one explores the surname field one may make even more startling, and possibly significant, discoveries.

For example, *Winders* is not a common name, yet such as bear it in these parts are not related by birth. Some two years ago, however, my patient Mr. *Winders* had gross cystic emphysema of the lower lobe of his left lung, and made an excellent recovery from lobectomy with great return of effort tolerance. Can one doubt, therefore, that when a year later a second Mr. Winders came along I had no hesitation in diagnosing "giant bullous emphysema" without even seeing the chest X-ray film, or in prognosing an excellent result from surgical excision?

Or consider again the name of *Ross*. On one occasion two patients aged 70 were in adjacent beds in my ward, and both bore the name of Ross. They had been schoolmates when young and had not seen each other since then. What was more astonishing to the uninitiated specialist (but not, of course, to the confirmed homonymo-diagnostician) was that both complained of dysphagia and both were suffering from carcinoma of the œsophagus. Have others a similar experience in other fields?

• • •

Some of us find it difficult to ensure that all our needs will be covered in the annual estimates. But a colleague, skilled in committeemanship, tells me that it's really very simple. All you need do is to put down some expensive but ostensibly necessary piece of equipment, such as a cerebroscope, costing say £500. In due course you say that the expansion of work in your department has made necessary the purchase of three neuroscopes, costing £100 each, and that you are willing to forgo the purchase of the cerebroscope. The committee is so pleased at saving £200 that your request goes through without trouble. At least that's the theory. But when I try that sort of thing I find that the money has already gone to provide a psychoscope for one of my rivals, or for repainting his ward, so that he can try out his crazy scheme of colour therapy. And some of the committee members are becoming a little suspicious at the annual appearance in the estimates of the cerebroscope.

Letters to the Editor

PANDORA'S BOX

SIR,—Whatever value the statistics on crime may have, attention must be drawn to some associated aspects of the social revolution in our island in the past two generations.

Fifty years ago 1 child in 8 died before its first birthday. Allowing for the general mortality from infectious disease, a disproportionate number died from neglect, in socially broken homes. Today those babies, protected and supported by preventive medicine and the medico-social services, survive to adolescence and eventual parenthood in the same antisocial family environment of the broken home. Many of them survive to roam as hyenas in our asphalt urban jungles.

Fifty years ago the targets of slum clearance had not been raised to the wholesale alternative provision by huge municipal estate agencies of widespread suburban semi-detached houses of lower-middle-class standard.

In those days the evils of life in poverty in closely packed slums created out of necessity a distinctive tribal community existence with traditions and taboos that at once supported and controlled its weaker members.

By our well-meaning efforts we have destroyed this gregarious community life and replaced it by an anonymous lonely personal life on amorphous housing-estates. There is a vast social difference between the doorstep gossip and constant traffic through the ever-open doors of a terraced slum street and the enforced separation of fourteen semi-detached houses to an acre.

We are in the same process in this country that is occurring in Africa. The new universal material success of the mid-twentieth century is destroying the steadying effect of former tribal custom, structure, and discipline.

It may well be that having broken up our older communities we will create them afresh through new links. Perhaps a television set in every home *is* preferable to a bathroom. Local community roots may grow again in a different fashion if every town is allowed its local transmission station.

At this time of social change not dissimilar to the Industrial Revolution of two hundred years ago we ought to be considering mental and spiritual needs and not remain content with improved standards of physical health alone.

Health Department, Brighton. W. S. PARKER.

ARTERIAL INJURY, REPAIR AND DEGENERATION

SIR,—The tendency today is to attribute arterial diseases, in young adults, to some relatively sudden degeneratory change. Hence the search for recent causes and the hope placed in such measures as regulating the intake of fats. There is reason to think, however, that these diseases are often the result of arterial injuries early in life.

Previously my colleagues and I have pointed out that, though single acute injuries to arteries heal directly like cutaneous wounds, their repair is much slower (Poole, Sanders, and Florey [1] have recently shown that stripped rabbit aortic endothelium is not completely regenerated even after 7 months). Consequently scar tissue may produce arterial rigidity, stenosis, and contracture long after the initial insult,[2 3] and we have come to believe that some forms of arterial disease may originate in a single injury, whose results are detectable clinically only 10–15 years later.

Our studies of vascular lesions in lathyrus intoxication in rats [2 4 5] have indicated (1) that the aorta is maximally sensitive to this toxin when growing at its greatest rate (in rats about 25–30 days after birth) and (2) that the greater sensitivity of the aorta at this time is due to the remodelling of the elastic membranes essential for their growth in length and diameter. It seems possible that the arteries of man, too, may likewise be maximally sensitive to injury during periods of greatest growth with its associated remodelling of arterial components—especially of the more intimal elastic membranes which seem, in rats, to lyse more rapidly and frequently.

There seem to be three periods of rapid body growth, and therefore arterial growth in man—namely, the last trimester of pregnancy, the first year or two after birth, and then (greatest of all perhaps) between the ages of 12 and 20.[6] On this basis it might be expected (1) that early and mild arterial lesions would be found in the very young, increasing in incidence during adolescence; (2) that malnutrition during such active vascular growth and remodelling would favour greater or more frequent injuries; and (3) that true fibrosis of these early lesions would supervene only 10–15 years later. Moon [7] has found that intimal lesions are quite common under the age of 20, and thinks that they are "identical with the early nonlipid phases of arterial sclerosis in adults".

Now Holman et al.[8] find (1) that the incidence of aortic lesions increases between the ages of 13 and 18 more than at any other age they studied, and (2) that the lesions in adolescents are mainly intimal "fatty streaks" without fibrosis. They believe that it probably takes 10–15 years for the early lesions of adolescence to fibrose. Their data, taken in conjunction with our own findings,[3 5 9] indicate that injuries to vessels in adolescents may culminate in localised fibrosis, hardening, and subsequently in further deterioration, perhaps in the manner outlined by us.[2 3 5] Mucopolysaccharides which accumulate in injured sites (before collagen synthesis) may have an important role both in precipitating circulating lipids and in binding them in the sites of repair.[10 11 12] The initial injury to vessels during their periods of active growth could result from deficiencies in nutrition, from physical overexertion, from any acute illness, or from metabolic derangement.

All the above facts together suggest the need for a reorientation of studies of the ætiology and pathogenesis of degenerative arterial diseases. In particular, the role of postnatal vascular growth and remodelling, and the injuries caused by derangements thereof, deserve more attention. It now seems desirable to discover, first, how the intimal lesions (which may be attendant on growth changes) can be prevented or at least lessened, and secondly how to retard if not prevent the deterioration of these early lesions into atheromatous plaques, intimal erosions with complicating fibrin deposits, and mural thrombi which may culminate in occlusions.

Appreciation of the amazing capacity of uterine vessels to recover from endarterial thromboses (after the onset of

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12. Gillman, T., Naidoo, S. S. *Endocrinology*, 1958, **62**, 92.

another pregnancy)[13] and the possible susceptibility of the aorta to remodelling and even to dissecting aneurysms during pregnancy,[14] as well as the subtle effects of endocrine glands on intermediate fat metabolism, plasma fibrin, and fibrinolysins,[11 12 15] may perhaps throw light on at least two apparently distinct aspects of vascular diseases—namely, (1) mural injury leading to sclerosis and later to lipoidal degeneration of the scars, and (2) intimal fibrin deposits with mural thrombi, progressing to stenosis and ultimately to occlusive episodes.

The approach here suggested may permit an explanation of the paradoxical frequency of arterial lesions in Africans, as described by Laurie and Woods [16] (and others quoted by them), and the rarity of coronary occlusive episodes among these people.

The African is probably at least as susceptible as the European to the early arterial injuries attendant on deranged remodelling and vascular injury during active growth. However, the deterioration of such injuries, and especially intramural lipid accumulations, intimal fibrin deposits, and mural thrombi might be expected to proceed more slowly in Africans, while the separate thrombotic process (e.g., in coronaries), with occlusions, could also be expected to be rarer though coronary lesions are common. For the Africans' diet is low in fat; moreover, we have now confirmed our previous finding [15] that adult African males have more active circulating fibrinolysins than European males, and this might decrease their susceptibility to intimal deposits and even perhaps to thrombotic episodes generally. On the other hand, the early (adolescent) lesions in Europeans might be expected to undergo fatty deterioration and culminate in thrombotic episodes more often, and at an earlier age, by virtue, respectively, of the Europeans' higher and more regular fat intake and their generally less active plasma fibrinolysins. This may be partly due to the full metabolic effects of uninhibited masculinity expressed in greater growth and physical activity, and perhaps, as in rats, in less efficient handling of ingested fats and lower circulating plasma fibrinolytic capacities than in females.[11 12] Similar factors may explain the differences in the incidence of advanced lesions and occluding thrombi in the coronary arteries in young Americans compared with Japanese.[17]

As for the deterioration in the aged, leading to the vascular sclerosis characteristic of senility, this (as has been shown elsewhere [9]) seems to be an entirely different process—namely, the gradual deterioration, with ageing, of vascular regeneration into repair.[9 18]

Schlesinger Organisation
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Department of Physiology,
Medical School, University of Natal,
Durban, South Africa. THEODORE GILLMAN.

AN INEXPENSIVE PHOTOCOPYING UNIT

SIR,—Professor Kark and Mr. Lockett's description of their photocopying unit prompts us to describe one which can be used in daylight.

It is a wooden box measuring 4 in. × 8 in. × 10 in., and containing twenty 24-volt festoon bulbs. The light passes through a yellow screen and plate of 'Perspex' and then enters an inflatable 'Polythene' bag. When a picture is to be taken, the subject matter lies face upwards, and a piece of slow autopositive paper face downwards is laid on it. The box is then pressed down by means of a strong handle fixed to its upper surface, and the paper exposed for about thirty seconds by means of a press-button switch.

When a suitable number of papers have accumulated in a light-proof carton, they are developed and used as negatives for the final prints obtained in a similar manner.

The quality of the prints is improved if a sheet of black paper is placed beneath the page to be copied. We have used this method for over two years, and can recommend its cheapness and simplicity of working.

Department of Physiology,
Royal College of Surgeons of England,
London, W.C.2. C. H. REDMAN
F. E. WEALE.

IMMUNOLOGY OF CANCER

SIR,—The recent revival of interest in the immunology of malignant disease brings to my mind a little known but interesting phenomenon—the development of "immunity" towards further tumour implants in experimental animals undergoing chemotherapy or other forms of treatment that result in complete regression of the tumour. This observation which, it seems to me, deserves wide attention has been made by a number of independent workers during the past decade, incidental to their main investigations.

Thus, in 93% of the mice bearing Ehrlich's adenocarcinoma, when treated with mycetin from the culture medium of *S. felis*, complete regression of the tumour was observed and the animals became resistant to further implants of this tumour.[1] Transplanted lymphomas in mice, treated with colchicine, permanently regressed, and immunity towards this tumour developed.[2] Complete regression of lymphosarcoma transplants was observed in mice receiving a combination treatment consisting of riboflavine deficiency and cortisone.[3] 70% of rats bearing Flexner-Jobling carcinoma when treated with triethyleneimino-s-triazine responded with complete destruction of the tumour and development of resistance to further implants of the same tumour.[4] When chickens with metastasising lymphomatosis were infected with Russian summer and spring encephalitis, louping-ill, and Japanese encephalitis, the tumour quickly regressed and immunity developed.[5] Ligation of methylcholanthrene-induced tumours in mice produced regression and immunity to further implants. Spontaneous tumours, however, when destroyed by ligation, did not produce immunity to later implants of the same tumour.[6 7] When tumour tissue mixed with adrenaline was implanted, the implants were resorbed and resistance to the same type of tumour developed.[8] Complete regression of leukæmia in mice under treatment with polycarbonyl compounds was accompanied by immunity to further implants.[9]

It is apparent from the many different measures which eventually result in refractoriness of an experimental animal to a specific tumour that this phenomenon is not in any way related to the agent by which tumour-regression is achieved; it apparently depends on two factors: (1) the gradual but complete destruction in situ of the tumour; and (2) the presence in the animal of an unimpaired or at least not permanently damaged immunological response system. The importance of this point is well illustrated by the ligation experiments of Foley,[6] in which the transplanted but not the spontaneous tumour gave rise to immunity in the experimental animal.

The immunological response system in animals may be adversely affected by the presence of a growing tumour [10] and it may be argued that this defence mechanism in animals bearing spontaneous tumours is permanently impaired while that in animals with transplanted tumours is only temporarily affected. Indeed, the development of a spontaneous tumour

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may be regarded as the result of a specific, but as yet unknown, type of immunological defect arising gradually and being amplified in a vicious circle by the growing tumour cells, while the experimental tumour may cause only an inhibition of the normal immunological defence system, thus avoiding destruction by the system.

It is now tempting to speculate that autolysing tumours may release certain immunologically active breakdown products giving rise to antibodies and thus immunity against further implants in animals with an intact immunological defence system, while similar antigens released in animals with spontaneous tumours and permanently impaired immunological defence mechanisms would be without effect.

A search for antigenic materials in tumours undergoing autolysis and their evaluation in the production of specific anti-tumour hyperimmune sera seems to hold much promise. Immunological and biochemical investigations of the possible presence in tumour tissue or host circulation of a substance capable of blocking or inhibiting normal immunological reactions might be equally profitable.

California Corporation for Biochemical Research, Los Angeles. H. RINDERKNECHT.

WATER FLUORIDATION

SIR,—Your correspondent (Oct. 4) exaggerates the difficulty of giving the public water-supplies with an optimum fluoride content. The Andover Corporation was not forced by legal difficulties to cease supplying such water; it did so because its constitution changed so that the majority of councillors no longer wanted to have the fluoride controlled by additions at the waterworks. Nor is there reason to suppose that the East Worcestershire Waterworks Company will wait until Parliament grants a power or imposes a duty on it " to add fluoride *or anything else* to a public supply " (my italics). It has a duty to supply wholesome water but is or claims to be uncertain whether this duty includes the right to add fluoride. So far there has been no official ruling that the fluoride content affects the " wholesomeness " of water although all the expert bodies that have considered the matter have said in effect that water fluoridated either in the ground or at the waterworks to 1 to 2 parts per million is more conducive to health than that which is fluoridated much less or much more.

The idea that some fanatics want the power to supply medicines, &c., with the water-supply is an ingenious fiction which your correspondent seems to accept as a fact. Disinfectants may be necessary and fluorides are normally present in all supplies, but no-one wants to put drugs in the water. The public still do not realise that fluoridation at the waterworks is, in effect, exactly the same as what has always happened in the ground except that it achieves a constant and standard fluoride content suitable to the climate and eating habits of the country, instead of a variable one determined by pure chance. If the public really believes in a " mystic spa-like power " in ordinary water it should be easy to convince them that fluoride is one of the most valuable elements in it.

The comparison between voluntary vaccination and " compulsory " fluoridation is entirely false. Being vaccinated is a slight but definite nuisance and risk, but voluntary use of a public supply containing fluoride involves no discomfort or risk whatever.

Explaining the value of an optimum fluoride intake is not " blinding the public with science " but enlightening them, and it is the necessary preliminary to any method of preventing fluoride deficiency. The suggestion that fluoridation is only acceptable to unsophisticated people is, perhaps intentionally, ludicrous. Americans are more hardened than any other people to high-pressure salesmanship, yet it is they who have progressed far ahead of us in achieving more wholesome water-supplies, not the backward peasantry of Europe or Asia. By all means let vanity be the motive for wanting better health, but let us try to catch up with those who excel us in public-health work as well as in flashing smiles, flashy cars, and racing yachts.

As for the suspected " definite disregard for minority views " it is puzzling to see how a public water-supply can satisfy both a minority and a majority who differ in their views as to the proper chemical composition or methods of maintaining it.

London, S.W.10. R. B. D. STOCKER.

TREATMENT OF INTERMITTENT CLAUDICATION WITH VITAMIN E

SIR,—Mr. Livingstone and Mr. Clifford Jones (Sept. 20) report a controlled trial which was entirely favourable to the use of vitamin E for intermittent claudication. Some five years ago you published a similar controlled trial,[1] made at the suggestion of the Medical Research Council, which produced exactly the opposite result. This is surely an interesting situation.

The significant difference between the two trials lies in the duration of treatment. In the original publications by Prof. A. M. Boyd and others,[2] one of the main points was that the treatment had to be continued over a long period—probably for at least six months—to obtain good relief. Livingstone and Clifford Jones' patients were treated for forty weeks, and the findings of Boyd were confirmed. Why then did the M.R.C. trial give treatment for only twelve weeks?

The unfavourable report, backed by the official standing of the M.R.C., probably deterred many practitioners from giving effective treatment to their patients. This seems to me to call into question the method of planning such trials, and whether the recognition of the M.R.C. as the official or last word in such matters is justified. The new trial has re-established the importance of vitamin E in intermittent claudication; but reversal of the adverse verdict has taken five years.

Hampton, Middlesex. MAURICE GOLD.

CHILDREN IN HOSPITAL

SIR,—I should be grateful for an opportunity to reply to Dr. Kidd (Sept. 27). I am glad he agrees with me on many points. If he came and spent some time at this hospital we might even convince him fully! I in turn would readily admit that the child in the film *A Two-year-old Goes to Hospital* is thoroughly unhappy. But we must remember that this film was made to convey a message; in real life one meets such extreme reactions only very rarely.

I laid myself open to being misunderstood by my choice of words when I wrote that our patients grow up into well-adjusted adults who stand out because of their quiet, non-complaining behaviour. I beg Dr. Kidd to believe me when I say that we can distinguish between patients who are quietly cheerful and those who are quietly miserable.

Dr. Kidd has conceded that patients over five years and certainly those over eight years of age can do with infrequent visiting. Dr. Librach writes (Sept. 27) that daily visiting has made little difference to his patients.

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2. Boyd, A. M., Ratcliffe, A. H., Jepson, R. P., James, G. W. H. *J. Bone Jt Surg.* 1949, **31B**, 325.

Miss Stephen and Dr. Whatley in a thoughtful review of the subject (Sept. 20) have come to the conclusion that for the great majority of children admission to hospital is not the tragedy it has been depicted. Prof. Bryan McFarland has expressed the same opinion in a recent letter to the *Manchester Guardian*.

Perhaps we can now view this whole problem with a little more detachment. I consider it an exaggeration to use the resources of the Health Service to admit father, mother, brother, and sister with the patient, as was advocated by Dr. Jacoby (Aug. 2), especially when in some parts of the country hospitals have emergency beds down the centre of the ward almost routinely.

King Edward VII Orthopædic Hospital, Rivelin, Sheffield. E. G. HERZOG.

SPERMATOGENIC MATURATION ARRESTS AND THE MALE ADRENOGENITAL SYNDROME

SIR,—Although the clinical picture of the adult adrenogenital syndrome in the female is well documented, the disorder is recognised so rarely in the male as to lead to the suspicion that it may often be overlooked. This report raises the question whether or not the syndrome in the male may be manifested by infertility associated with the testicular histological picture of spermatogenic maturation arrest.

Case-report

In August, 1955, a 28-year-old white man was referred for consultation because of infertility. He and his wife had been married for 5 years and conception failed to occur for 4 years. The wife, who had had irregular periods, had been examined by a gynæcologist and found to be of "low fertility". The patient had seen several urologists who, on the basis of examinations of the seminal fluid, informed him that he had "very few sperm". He had been placed on various medications, including 'Proloid', without improvement. Testicular biopsy had been performed in November, 1954, and he had been told that he had "maturation arrest" of spermatogenesis. He and his wife had recently consulted the referring gynæcologist who had found a sperm-count of "1000". The past illnesses included a questionable history of mumps in childhood and some allergies, but was otherwise non-contributory.

He looked a normal man and weighed 180 lb. The blood-pressure was 110/70 mm. Hg. The testes were normal in size and consistency. No abnormality was noted in the prostate or the secondary sexual characteristics.

The urine was normal. The serum protein-bound iodine was 5·4 μg. per 100 ml. The urinary excretion of the neutral 17-ketosteroids was 14·6 mg. in 24 hours. The testicular biopsy sections (see figure) were reviewed by Dr. Arthur R. Sohval:

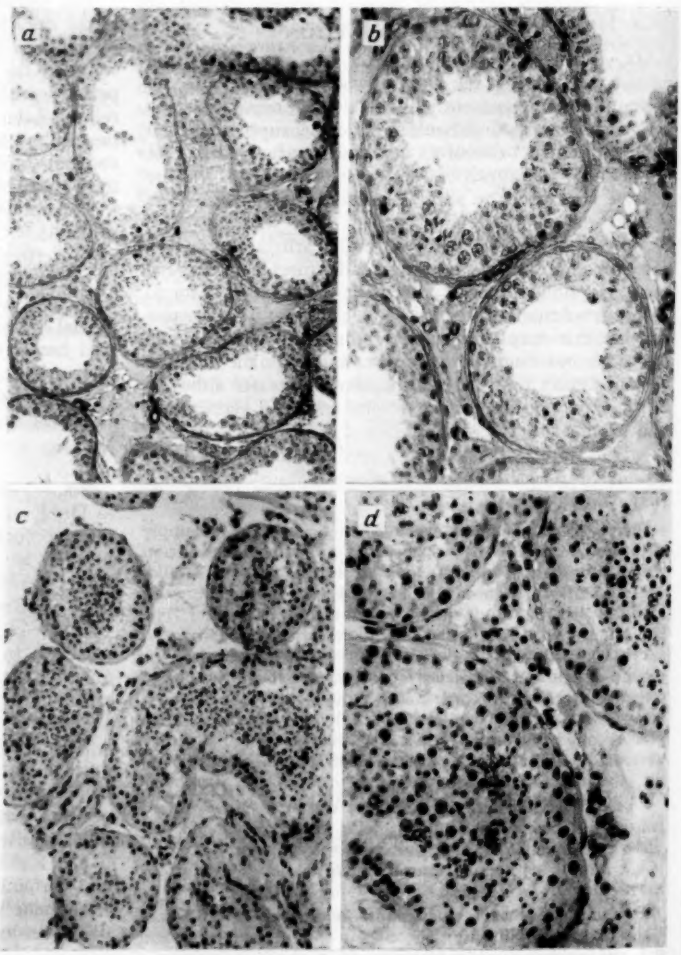
Right testis: In general, the tubules were somewhat subnormal in size and their cell population was moderately reduced. Spermatogenesis in the majority of tubules was arrested at the spermatocyte I stage. Disorganisation of the seminiferous epithelium and excessive sloughing of immature elements were present. Occasional tubules contained secondary spermatocytes and a few spermatids. Infrequent spermatozoa were seen in some of these tubules. The intertubular connective tissue tended to be hyalinised. Normal-looking Leydig cells were present. These were chromatin-negative.

Left testis: Same findings (without hyalinisation of intertubular connective tissue).

Diagnosis: Maturation arrest, predominantly at the primary spermatocyte stage.

Because of reports claiming a "testosterone rebound phenomenon", he was advised to take testosterone propionate intramuscularly (100 mg. twice a week for 12 weeks). After some delay, this was given from June to August, 1956. Re-examination of the seminal fluid 1 month after completion of the course showed no change. At this time, because of a speculation that the clinical picture might represent a manifestation of the adult male adrenogenital syndrome, he was placed on prednisone by mouth (5 mg. four times a day). Three months after the start of treatment with prednisone, the gynæcologist reported marked improvement in the sperm-count. Testicular biopsy was performed again (Feb. 17, 1957) $4^1/_2$ months after the start of treatment with prednisone. The specimen was examined by Dr. Sohval:

Right testis (see figure): A normal testis showing active spermatogenesis with full spermiogenesis in the great majority of tubules. In comparison with the sections of 1954, the tubules were larger and the seminiferous epithelium was considerably more abundant. The intertubular connective tissue was correspondingly smaller in



Testicular biopsies: (*a*) right testis prior to treatment (×100); (*b*) right testis prior to treatment (×400); (*c*) right testis following treatment with cortisone (×100); (*d*) right testis following treatment with cortisone (×400). See text for description.

CHANGES IN SPERM-COUNT DURING TREATMENT WITH PREDNISONE

Date	Volume (ml.)	Sperm-count (million per ml.)	Total count (million)	Motility (% active)	Prednisone	Comment
1954 Nov. 22						Testicular biopsy (fig. *a* and *b*)
1955 August 8						Sperm-count " 1000 "; 17-K.S. 14·6 mg.
1956 June 15						Testosterone propionate 100 mg. twice weekly
Aug. 15						
Sept. 19					Started 5 mg. q.i.d.	Sperm-count unchanged
Oct. 25						17-K.S. 7·6 mg.
Dec. 10					5 mg. q.i.d. × 2½ mos.	Sperm-count " markedly improved "
1957 Jan. 7					5 mg. q.i.d. × 3½ mos.	Sperm-count as on Dec. 10, 1956
Feb. 17						Testicular biopsy (fig. *c* and *d*)
Feb. 21	4·2	3	13	15	5 mg. q.i.d. × 5 mos.	Very low sperm-count, poor motility and morphology
April 8	3·6	13	47	15	5 mg. q.i.d. × 7 mos.	Low sperm-count, poor motility
April 11					Start 5 mg. b.i.d.	
April 22					Stop prednisone	
May 15	2·4	9	22	10	Off 1 mo.	Low sperm-count, very poor motility
Sept. 4	3·2	2	7	0	Off 5 mos.	No motility, occasional dead cell
Sept. 11					Start 5 mg. b.i.d.	
Oct. 30	2·3	4	10	Few active	5 mg. b.i.d. × 6 wks. Start 5 mg. t.i.d.	Very low sperm-count, occasional active cell
1958 Jan. 6	3·0	8	24	10	On 5 mg. t.i.d. Start 5 mg. q.i.d.	Very low sperm-count, very poor motility
March 26	3·2	4	13	20	5 mg. q.i.d. On prednisone 6½ mos.	Low sperm-count, low % active cells
April 9	2·0 (split 1st part)	40	80	10	5 mg. q.i.d. On prednisone 7 mos.	First part ejaculate, passable sperm-count, poor motility
June 17	1·2 (split 1st part)	42	50	30	5 mg. q.i.d. On prednisone 9 mos.	Passable count per ml., low % active cells, 17-K.S. 4·5 mg.

amount. It was not hyalinised. Leydig cells were normal in number and appearance and were chromatin-negative.

Examination of the seminal fluid was then carried out by Dr. John R. McLeod who performed all subsequent sperm counts. The findings are shown in the accompanying table.

Since the administration of testosterone could not be excluded as a cause of the striking improvement, it was decided to stop treatment with prednisone and to start it again later. As can be seen from the table, the sperm-count deteriorated when prednisone was withheld and then markedly improved when prednisone was again administered. In the last two specimens obtained, only the first part of a split specimen was examined since artificial insemination with such a split specimen was contemplated. Nonetheless, the total count and motility had improved and the concentration of sperm was 40 million per ml.

Discussion

In youths with congenital adrenocortical hyperfunction associated with virilism, maturation of the testes may proceed as far as the production of spermatocytes, the seminiferous tubules being lined by germinal epithelium.[1–3] In a study of 6 such patients Wilkins and Cara [2] noted that, in the younger age-groups, the tubules were small and lined by layers of undifferentiated cells and a few spermatogonia. In the older patients increased numbers of spermatogonia were present and even spermatocytes and Sertoli cells were seen. It is of interest that in a 25-year-old untreated male with congenital adrenocortical hyperplasia, the testicular biopsy revealed development only to the stage of spermatocytes.[2] Although in a case reported by Goldberg interstitial cells were present, no Leydig cells were encountered in the specimens reviewed by Wilkins and Cara.[2] In the group varying in age from 6 years 9 months to 8 years 9 months reported by Wilkins and Cara, treatment with cortisone was followed by complete maturation of the testes to the stage of active spermatogenesis.

It is generally accepted that the virilisation associated with congenital or acquired adrenocortical hyperplasia is arrested by cortisone. In view of the resemblance of the histological picture in the testes of the patient described here to that seen in patients with congenital adrenocortical hyperfunction, and in the light of the striking similarity in maturation of the testes following the administration of prednisone, it does not seem unwarranted to suspect a similar ætiology. One hypothesis is that the syndrome of infertility, oligospermia, and the testicular histological picture of spermatogenic maturation arrest may represent a form of the adult adrenogenital syndrome.

It is extremely unlikely that the improvement in the sperm-count reported here represents a so-called testosterone rebound phenomenon. According to Charny,[4] this phenomenon occurs within 2 to 3 months after testosterone withdrawal and peak improvement is noted in 4 to 5 months. Heckel and McDonald [5] reported the rebound within a year and in one rare instance as long as 72 weeks after testosterone administration

Cortisone has been previously used in the treatment of infertile males.[6–8] In most instances, however, insufficient details are given for proper evaluation, but two striking points may be noted from a review of the reports:

(1) The one patient who responded to treatment with cortisone in the series reported by Michelson and his associates [7] had maturation arrest on testicular biopsy. Although other patients in this study had a similar lesion it is possible that the course of treatment was too short for improvement to ensue.

(2) Very recently, Perloff and Hadd [9] reported a 36-year-old man with an adult " virilising type " of adrenogenital syndrome. He had an increased urinary excretion of neutral 17-ketosteroids, and a low sperm-count (20 million), with decreased motility. Following treatment with cortisone the sperm-count improved greatly. It is of interest to note that the testicular biopsy performed prior to treatment showed the sections were normal excepting for some impairment in spermatozoal maturation!

Mount Sinai Hospital,
New York. J. LESTER GABRILOVE.

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9. Perloff, W. H., Hadd, A. E. *Amer. J. med. Sci.* 1957, **234**, 441.

GALEN IN CHINA

SIR,—Dr. Hoenig (Oct. 11) takes me to task for my pessimistic explanation of the official encouragement given to the traditional physic of China. He offers a simpler interpretation, and points to apparently similar movements supported by the non-Communist Governments of India and Ghana. But these movements lack an essential feature of the happenings in China.

In India and Ghana the support for the old does not involve a simultaneous assault upon the new. There is no question of Ayurvedic theory becoming a required subject in the curriculum of the Indian medical colleges; neither does the Indian Medical Association castigate its members because they do not show sufficient admiration for the ancient lore.

I tried in my article to stress the changes in attitude being forced upon Western practice in China. It is this that demands notice, and not the simple sight of old traditions getting State support.

In Hong Kong there is a charity hospital receiving a substantial annual Government grant. The sick poor who go there choose whether they will take Chinese or Western treatment, for both are provided. For this phenomenon I happily accept the sort of explanation offered by Dr. Hoenig. For what is happening in China, no such ready-reckoning will do.

Dr. Hoenig may well be right in feeling that my own explanation would sound rather silly to doctors in underdeveloped countries. I don't know. Whenever I tried to talk to doctors in China about it, they became silent. But I have the impression that their silence covered doubts as disturbing as my own.

Department of Physiology,
University of Malaya,
Singapore, 3.

DONALD GOULD.

RECTAL EXAMINATION

SIR,—There are two reasons why a rectal examination is sometimes deferred or evaded in the surgery or home.

A normal reluctance to affront the modesty of the patient has first to be overcome and this is more difficult when the patient is known socially by the doctor.

In addition, the practical difficulties of the investigation are occasionally a deterrent. Although it is preferable to avoid any contact with fæces by the use of a rubber glove or skirted finger-stall, the thick rubber of which these are made blunts the finer sensations of touch. Furthermore, the washing and boiling of gloves at the end of the day is not the ideal prelude to dinner; and if the forgotten steriliser boils dry the result may long be remembered.

Most doctors therefore use the " disposable " finger cot, wrapping gauze or cotton-wool around the proximal phalanx. This gives a sense of security, but not always complete protection.

Fig 1.

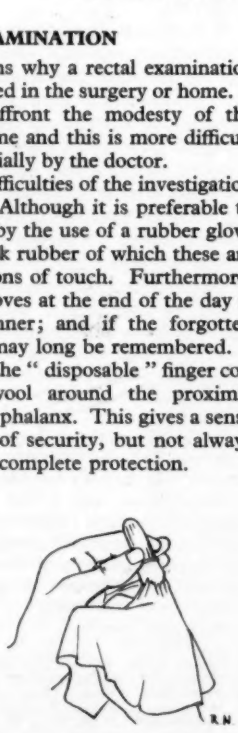

Fig 2.

After experiments with greaseproof paper bags, ' Cellophane ' wrappers, and other protective devices, I offer the following technique which has proved simple, economical, and efficient.

(1) *Two* face tissues are picked up by the middle and 1/4 in. is torn off the apex (fig. 1).

(2) The finger is put through the hole and the tissues are moulded round the proximal phalanx.

(3) A medium or large finger cot is rolled down over the tissues. It should overlap for an inch (fig. 2).

(4) When the finger is removed from the anus, the skirt of the tissues is used to strip the cot off. It may also be employed for removing excess lubricating jelly from the anal margin, and is safely disposed of down the water-closet or in the furnace.

Finger cots are best ordered in medium and large sizes. They are cheaper by the gross.

The line drawings were made by Mr. Richard Neave, assistant artist to Middlesex Hospital Art Department.

Middlesex Hospital,
London, W.1.

J. H. LEES FERGUSON.

TETRACYCLINE IN CHRONIC BRONCHITIS

SIR,—In the paper by Dr. Buchanan and his colleagues (Oct. 4) on the value of long-term administration of tetracycline to chronic bronchitics it was noted that at the end of the trial period of one year, during which each patient received 500 mg. of tetracycline daily, 3 out of the total of 21 patients treated harboured tetracycline-resistant *Staphylococcus aureus* in their anterior nares. Regular examination of the nasal and fæcal flora for the presence of *Staph. aureus* was, however, not undertaken. Recent work in this department on a somewhat similar series of cases is relevant in this connection.[1]

10 children with a history of acute rheumatism were given prophylactic tetracycline (' Achromycin ') in a dosage of 250 mg. daily for periods of from eight to twelve months. The children were treated at home but were required to attend an outpatient clinic in the National Children's Hospital for review at approximately monthly intervals. During the course of the trial regular examination of the nasal and fæcal flora for *Staph. aureus* was carried out, and the strains isolated were tested for sensitivity to tetracycline, penicillin, and streptomycin. Before the trial began nasal swabs from 9 cases and fæces from 6 cases were also examined. Of these 15 pre-treatment specimens 1 (a specimen of fæces) yielded a tetracycline-resistant strain of *Staph. aureus*. (This strain was resistant also to penicillin and streptomycin.) During the trial 7 cases at some time yielded a tetracycline-resistant isolate; in 6 cases this occurred on two or more occasions. The total number of isolates and the number of these which were tetracycline-resistant (together with the findings in a control series of 10 cases also with a history of acute rheumatism—who were given an inert preparation) are shown in the accompanying table.

FREQUENCY OF ISOLATION OF *Staph. aureus* FROM TREATED AND CONTROL CASES

—	—	Treated cases	Controls
Nasal swabs	Total no. of specimens	76	60
	Isolations	40*	29†
	Tetracycline-resistant	16	1
Fæces	Total no. of specimens	48	44
	Isolations	24	10
	Tetracycline-resistant	18	2

Sensitivity tests not carried out on: * 3 strains; †1 strain.

The data show that tetracycline-resistant strains were isolated with much greater frequency from both the nasal

1. Stewart, F. S., Crennell, R., Doyle, E. E. *Irish J. med. Sci.* March, 1958, p. 142.

swabs and fæces of the treated cases than from those of the controls. Of particular interest was the finding that the total frequency with which *Staph. aureus* was isolated from fæces was also appreciably higher in the treated cases. No significant difference between the two series was observed in the frequency of nasal carriage.

A majority (23 out of 34) of the tetracycline-resistant isolates from the treated cases were resistant also to penicillin or to penicillin and streptomycin. It seems probable, therefore, that these strains were picked up from the hospital environment and that the risk of selecting for resistant organisms might have been less if the patients had been treated entirely in their own homes. The results obtained nevertheless emphasise the potential danger of prolonged antibiotic administration in increasing the prevalence of resistant strains. They suggest also that the fæces of patients under treatment may be a more serious source of dissemination of such strains—at least as far as tetracycline is concerned—than the nasal secretions.

Department of Bacteriology,
Trinity College, Dublin. F. S. STEWART.

RECTAL AND SUBLINGUAL HEPARIN

SIR,—In the department of medicine of Alexandria University, we have often noticed prolongation of the clotting-time after subcutaneous or intramuscular injection of heparin sodium 1 ml. (25,000 I.U. *U.S.P.*). The effect was irregular and unpredictable, unlike that achieved by the intravenous route. Heparin as a suppository was tried in eight adult patients in hospital. The capillary-tube clotting-time was estimated every 15 minutes for 5 hours. Samples of the same batch of heparin were given intravenously to the same patients as a control, and as the coagulation-time was then significantly prolonged (i.e., to 10 minutes or more) the heparin used was considered potent.

Groups of heparin suppositories were prepared with a constant volume of heparin solution (25% of the total mass). Each suppository weighed 4 g. At first a solution containing 5000 units per ml. was used, and later one of 25,000 units per ml. Thus, each suppository contained either 5000 units (i.e., 50 mg. heparin) or 25,000 units (i.e., 250 mg. heparin). Cocoa butter was used as base in the first trials. It was warmed and then the heparin solution was incorporated. There was no prolongation of the clotting-time after either strength of suppository; and the weak form was discarded later on. Then, to hasten the rate of emulsification and absorption, either sodium lauryl sulphate or ethylene glycol was added to the mass. The capillary-tube clotting-time was increased by from 2·5 to 3 minutes after $^1/_2$ to 1 hour, and was raised for only $^1/_2$ hour. Lastly, cocoa butter was replaced by 'Ihaussen suppository excipient, type W', a new synthetic triglyceride fat, which has a high water-absorption capacity. It has a melting-point of 33·5–35·5°C (92–96°F) and a solidification-point of 29–32°C (84–89·5°F). No prolongation of the clotting-time above 3–4$^1/_2$ minutes was noticed in the eight patients, though in three of them two suppositories were administered each time (i.e., 500 mg. heparin). This is a very large dose, and very costly.

Warming the cocoa butter should not spoil the efficacy of heparin, since heparin can be sterilised by boiling or autoclaving at 110°C for not more than 30 minutes.[1] Therefore, most probably, heparin was not adversely affected during the preparation of the suppository. In spite of this, we thought of mixing heparin with shreaded cocoa butter in the cold and then moulding it. These suppositories produced no significant prolongation of the clotting-time.

1. Goodman, L. E., Gilman, A. The Pharmacological Basis of Therapeutics; p. 1142. New York, 1941.

Rectal instillation of heparin-sodium solution (both 5000 units and 25,000 units per ml.) again produced no appreciable absorption, and changes in the clotting-time were slight.

Sublingual heparin tablets, containing heparin 10 mg. and lipocaic pancreatic principle 20 mg. are sometimes advocated to diminish post-prandial hyperlipæmia. Five to ten tablets (a large inconvenient bulk), given to five patients caused no significant increase in the clotting-time; nor did instillation under the tongue of 1–5 ml. of the heparin solution (25,000 units per ml.) in four patients.

These limited data suggest that heparin is poorly absorbed from the rectal or oral mucous membranes and that heparin rectally or sublingually is not effective in prolonging the clotting-time. Lindewald [2] found that the higher the molecular weight of a substance the less its absorption from the rectum, and he reported that Primarius Lasch (Austria) had found that only 10% at most, of a rectal dose of insulin was absorbed. The monometric form of insulin has a molecular weight of 12,000 or even 6000.[3] The molecular weight of the heparin-lipoprotein complex found in mast cells is 100,000.[4] The very great molecular weight of heparin may explain the inability of rectal or oral mucosa to absorb it.

I am indebted to Dr. Abdel Khalek for his help in preparing the suppositories.

Faculty of Medicine,
Alexandria University. M. H. GHANEM.

BLANKETS AND INFECTION

SIR,—Hospital blankets are much in the news but their terminology in the medical press is confusing. Blowers et al.[5] referred to "loomstate cotton weave" and have been so quoted.[6] Your note [7] refers to "tufted towelling, cellular cotton, and turkish towelling". A questionnaire has been circulated which seeks to distinguish between terry towelling and turkish towelling. These terms have well-authenticated meanings in the textile industry; so it would be well for those who wish to discuss or to buy hospital blankets to use the terms accordingly.

Firstly, 'loomstate' is the condition of all woven cloths immediately after weaving and before any washing, bleaching, or dyeing process, so the term cannot possibly refer to any particular weave or fabric structure. The blanket which Blowers and others describe as 'loomstate' was evidently made from loomstate cloth but the structure of the fabric was cellular and produced by leno weaving. This type of blanket should therefore be described as a cellular-woven blanket or, perhaps preferably, as a leno blanket, and further qualified by the type of fibre and the finishing process—e.g., wool, dyed, or cotton, loomstate.

Secondly, towelling, whether rolled, tufted, turkish, or terry, is all basically the same weave. The adjectives tufted and terry are synonymous, but tufted is technically incorrect. Such towelling is made with loops in any of many variations of the terry weave. Blowers and others used bleached terry, or turkish (as you wish), towelling, with a long pile of fine yard and found it expensive and inefficient as a heat-insulating layer in bedclothes. Tufting, in the textile trade, connotes a process in which lines of cut or uncut loops of coarse yarn are formed in cloth after weaving, as in tufted bedspreads. The so-called "tufted blankets" used in the London Hospital were made by Ashton Brothers after extensive experiments to produce a blanket better than either the cellular woven blanket or the bleached terry blanket; but they have not been made by the

2. Czetsch-Lindewald, H. Suppository Book. Aulendorf, Germany, 1958.
3. Osol, A., Farrar, G. E. The Dispensatory of the United States of America; p. 682. Philadelphia, 1955.
4. Snellman, O., Sylven, B., Julen, C. *Biochim. biophys. Acta*, 1951, 7, 98.
5. Blowers, R., Potter, J., Wallace, K. R. *Lancet*, 1957, i, 629.
6. Schwabacher, H., Salsbury, A. J., Fincham, W. J. *ibid.* Oct. 4, 1958, p. 709.
7. *Ibid.* p. 743.

tufting process. They are terry blankets, but the weave [8] is arranged to give a pattern of indentations over both sides of the blanket so that when the blanket is used between sheet and counterpane the indentations form separate cells of air which are very effective insulators.

Technical Department,
Ashton Brothers & Co. Ltd.,
Hyde, Cheshire. A. W. BAYES.

SEPARATISM OR REINTEGRATION?

SIR,—Surely your statement last week that "in Britain at least, consultant appointments are not made on the strength of success in any examination" is something less than the whole truth?

Any aspiring consultant knows that failure to obtain an M.R.C.P. or an F.R.C.S. automatically disqualifies him from promotion to consultant physician or surgeon. Is this not the apotheosis of the examination? If, as we seem to believe, the proper yardstick for selection of our consultants is a series of high-school tests, is it not a fact that your statement misrepresents the real position?

It is to be hoped that pathologists will reject Dr. McMenemey's advice to submit themselves to this form of elimination and will not be diverted from their real job and training to pursue an irrelevancy which can have little meaning in terms of what is and what is not a good pathologist.

Department of Anatomy,
University of Glasgow,
Glasgow, W.2. G. M. WYBURN.

*** A longer quotation from our sentence would read: "In Britain at least, consultant appointments are not made on the strength of success in any examination (though such success may be one requirement) . . ." —ED. L.

SIR,—Your leading article overlooks the vital objection on the part of pathologists to the Royal College of Physicians—its constitution.

This calcified historical vestige—"anlage", of course, to pathologists—excites widespread disgust not only among pathologists but also among the many physicians who are merely members and even among some most distinguished fellows. Naturally, for reasons of self-protection in such a medieval society, open criticism, inadmissible it seems to the medieval mind, is restricted. The formidable intellect of one ex-president was, despite himself, moved to suggest the title "the Royal College of some Physicians" [9] for the College "at times". One of your most distinguished predecessors, Sir, observed "Who shall dare to utter such a word as 'reform' within the walls of the College in Pall Mall East?" (cited by Sir John Charles [10]). No doubt such tradition is worthily maintained, but today does not attract the young. Even Dr. McMenemey—a fellow and therefore allowed some voice in government—somewhat wistfully alludes to the inconvenient desire of pathologists for enfranchisement. Is the breath of freedom at last in the air? Even if all pathologists were by a stroke of the pen or by "published work" made members of the Royal College of Physicians, with the present constitution they would still have no effective voice in their own affairs; their governors would still be arbitrarily chosen and imposed by others. Thus the constitution is such as to produce among all men, still free, a determined vote of "no confidence".

If, to our regret, it should be conclusively proved at long last that it is impossible that pathologists should have a college, then let us grasp the warm and liberal hand of the surgeons, as so many others have done, but at all events let us spurn the cold and clutching hand of the physicians.

The Royal Hospital, Sheffield. J. L. EDWARDS.

8. Patent application 9787/58, registered design 469747.
9. *Lancet*, 1954, i, 167.
10. *ibid.* p. 455.

BANTING UP TO DATE

SIR,—We would be grateful if we could have space in your columns to divest ourselves of a mantle which we have neither sought nor, in the present state of ignorance, desire; that of advocates of a high-fat diet in the treatment of obesity. We have never advised such a diet for general use. We seldom prescribe it. Our interest in this subject has always been in the mechanism of differing rates of weight-loss in obese subjects over a short period, in response to isocaloric diets made up of different types of foodstuffs. In spite of your remarks in the leader of Oct. 11, our interest has continued because it appears to us that only 30–70% of this weight-loss can be accounted for in terms of available body-water and because certain aspects of metabolism in the obese differ from those in the non-obese.

It is curious to note how the medical profession has tended to follow the public in treating the subject of obesity on an emotional plane. It might be timely to remember that it was this attitude which did more than anything else to turn the word Banting from an undertaker's surname into a national symbol.

The Middlesex Hospital,
London, W.1. A. KEKWICK
G. L. S. PAWAN.

SIR,—Your leader of Oct. 11, discussing two books on preventing overweight, makes no effort to resolve this problem in terms of the Darwinian theory of evolution, which alone offers a permanent solution to it.

It is not always realised that Darwin originally advanced his theory to explain the remarkable adaptation of all living organisms to their natural environment. This adaptation, so universal and so constant, may be regarded as a law of Nature, and is, indeed, most conveniently referred to as the Natural Law of Adaptation. This law holds the whole answer to the problem of preventing overweight.

According to this law, the instinct of appetite can never be at fault, *as long as it is employed on natural substances*. No rabbit ever ate too much grass; no rook ever ate too many wireworms; no herring ever ate too much plankton; no wild creature is ever overweight. It is not the appetite that is at fault: it is the employment of the appetite on unnatural materials, when it becomes no longer reliable, that causes the trouble.

A simple example will make this clear. A bar of chocolate often contains more sugar than a dozen English apples. The instinct of appetite would indicate just when to stop eating the apples—say, after the third. But it cannot indicate just when to stop eating the concentrated chocolate. Who stops one-quarter the way along the bar?

Application of this law indicates that the cause of the overweight now so prevalent in civilised countries is indeed the consumption of carbohydrates—but only because these carbohydrates have been very greatly concentrated by machinery. This concentration is considerable even in the case of white flour, but in the case of sugar it is enormously greater, the 10% of sugar in the beetroot having been raised to 100% in the crystalline product. As long as the carbohydrates are eaten in their unconcentrated form—the starch in cereals and potatoes, and the sugars in fruits and vegetables—they are perfectly harmless, though careful application of this law excludes the use of honey and dates by the inhabitants of these islands.

The view that exercise has anything fundamentally to do with overweight is quite untenable.

Not only is this so according to the natural law of adaptation —which indicates that anyone should take only as much exercise as he desires—but it can actually be seen to be so in any zoo and in many private houses. In a zoo the two opposites of creation are seen imprisoned behind bars: a large animal, such as a tiger, accustomed to roam about in several square miles of jungle, is confined to a cage measured in cubic feet; and a small bird, such as a canary, accustomed to fly about over several acres of countryside, is confined to a cage measured in cubic inches. Yet in spite of having their natural exercise reduced to vanishing-point, each of these creatures, just because it continues to eat its natural food (in the one case raw meat and in the other case unaltered seeds) retains its natural weight. Strenuous exercise may reduce overweight, it is true, but it is a case of two wrongs not making a right.

Fat, taken in excess of the individual's natural wishes, increases the risk of contracting coronary disease, as I have tried to show in the small work referred to in my letter of Aug. 23. The consumption of fat, as accurately decided by a person's particular liking for this food, is in accordance with the law just mentioned, and is therefore perfectly safe (since no fat has been concentrated by man above the level found in the fat in ordinary meat); but its consumption in any greater amount is, according to this same law, asking for trouble.

In my experience the prevention of overweight by these natural means is simple; but the cure of an existing overweight is more difficult, and necessitates a preliminary period of partial starvation.

Gosport, Hampshire. T. L. CLEAVE.

EFFECT OF DIETARY FAT ON FAT CONTENT OF HUMAN MILK

SIR,—The nutritional status of the mother has long been held to affect the composition of milk, but the evidence on this point is not in fact conclusive. In order to investigate whether the dietary fat has any effect on the fat content of breast milk we analysed the diet and the milk of 175 lactating women of normal health belonging to different socio-economic groups. The interesting observation was that increases in dietary fat up to a certain requisite amount may increase the fat content of breast milk.

DIETARY FAT AND MILK FAT

Socio-economic group	Mean per-capita income per month (rupees)	No. of samples analysed	Dietary fat (g.)	Milk fat (g. per 100 ml.)
Group I (very poor) ..	6·1	45	28·13 ± 4·49	4·31 ± 0·16
Group II (poor) ..	15·7	45	59·98 ± 4·18	4·85 ± 0·19
Group III (middle class)	30·2	45	77·02 ± 4·96	4·78 ± 0·19
Group IV (upper middle class)	110·4	40	107·70 ± 5·48	4·80 ± 0·18

The samples for analysis were collected according to the procedure adopted by Kon and Mawson [1] and analysed for fat by the method of Chiba et al.[2] The diet survey of the lactating women followed the method of Pasricha.[3] The results are summarised in the accompanying table. Milk in group I contains significantly less fat than that in the other three groups, and this is reflected in the lower fat intake of group I.

The fact that the other three groups do not show any difference in milk fat suggests that increases in dietary fat beyond a certain amount may not result in increases in milk fat.

Our thanks are due to the Indian Council of Medical Research, for sponsoring this project, and to Dr. R. Rajalakshmi for her statistical guidance.

M. G. KARMARKAR
A. D. DEODHAR
J. KAPUR
C. V. RAMAKRISHNAN.

Biochemistry Department,
Baroda University, Baroda, India.

1. Kon, S. K., Mawson, E. H. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1950, no. 269, p. 75.
2. Chiba, K., Moriwaki, T., Suzuki, S., Hirai, N., Imahori, K. *Nat. Sci. Rep. Ochanomizu Univ.* 1956, **6**, 224.
3. Pasricha, S. *Ind. J. med. Res.* 1958, **46**, 605.

ORAL TREATMENT OF PERNICIOUS ANÆMIA

SIR,—We are grateful to Dr. Jerzy Glass (Oct. 4) for his rational and lucid criticism of our work.[1] If we could answer all his searching questions completely then the problems of pernicious anæmia would, of course, be at an end. We shall do our best with them, however, and hope for his indulgence if, in some of our replies, we have to introduce a little speculation. Our answers are given below in the order in which the questions were asked.

(1) Five of the six original patients [1] are still being maintained satisfactorily on daily doses of 10 μg. of vitamin B_{12} and in every case the average daily intake over the entire period of treatment is now less than 15 μg.[2] The sixth case, after 150 days' oral treatment, rather disappointedly elected to have injections "like her sister", who also suffers from pernicious anæmia, and who had been receiving parenteral treatment for years. Up to the time of transference her maintenance on oral therapy had been quite satisfactory.

(2) True nutritional vitamin-B_{12} deficiency is virtually non-existent in this part of the world, and there was nothing in the clinical history of the patients to suggest that these cases were not true examples of pernicious anæmia. If, however, we were to assume that nutritional causes account for as many as 5% of megaloblastic anæmias in this vicinity—which is a ridiculously generous estimate—then the odds against all six belonging to this category are more than sixty million to one.

(3a) We are, of course, well aware that resistance can develop in the oral treatment of this condition. It was this fact which made us decide to pay little attention to the initial responses, no matter how encouraging these might be. Furthermore, we deliberately refrained from publishing our work until most of the cases were past the critical first 6 months, during which period most cases of resistance appear. At the time of writing all five cases have been on treatment for over 500 days and are still perfectly well.

(3b) We have estimated serum-vitamin-B_{12} levels regularly on all patients since the beginning of our experiments. We have refrained from publishing them yet, however, because the results have tended on the whole to be higher than we expected, and we were not satisfied that our technique was completely above suspicion.

In the second half of his letter Dr. Glass asked four more questions about gastric proteolysis.

(1) Little is really known about gastric and pancreatic proteolysis, and therefore it is hazardous to presume—as Dr. Glass appears to do—that the two are necessarily identical or interchangeable. As man has been endowed with two such completely separate proteolytic systems, it is surely logical to propose that each has—in part at any rate—some specific role to play, although other functions might be common to both. After all, metaproteins, polypeptides, &c., embrace a whole range of substances which have relatively little in common apart from approximate molecular size. Furthermore, physiologists tell us that the first intermediate breakdown product of protein in the stomach is an acid metaprotein, whereas the pancreatic secretions produce an alkaline metaprotein. Are

1. Heathcote, J. G., Mooney, F. S. *Lancet*, 1958, i, 982.
2. Heathcote, J. G., Mooney, F. S. *J. Pharm. Lond*, 1958, **10**, 593.

these two substances identical? We think not. And if they are not identical is there any reason for presuming that the other intermediate breakdown products of protein—as produced by stomach and pancreas—are any more alike? In our view the essential proteolysis of bound vitamin B_{12} normally can occur only in the stomach and, although the mechanism is not yet completely understood, the fact that the pancreas cannot apparently produce the same effect is not a serious objection to that opinion.

(2) It would seem to us that the statement of Dr. Glass that "most of the patients with simple histamine-fast anacidity show an entirely normal intestinal absorption of vitamin B_{12} in the intestine" contradicts his own findings, as set out in the paper[3] which he quotes in support of this statement. According to our interpretation, figs. 2 and 3 in this paper show quite clearly that the average uptake of labelled crystalline vitamin is reduced in histamine-fast anacidity and hypoacidity. Indeed, in his summary of the paper, Dr. Glass says there may be "partial, incomplete defects in the intestinal absorption of vitamin B_{12} . . . in some of the patients with gastric anacidity, and in some of the elderly people with gastric hypoacidity". This reduced absorption of the crystalline vitamin is in agreement with the incidence of incipient megaloblastic erythropoiesis found in elderly achlorhydric patients despite the absence of manifest symptoms of pernicious anæmia.[4] Both of these facts, we believe, are in line with reduced proteolytic activity, although we are by no means committing ourselves to the view that only pepsin and cathepsin are the operative enzymes in gastric proteolysis. It is known that the stomach also secretes an aminopolypeptidase, a dipeptidase, and possibly a prolinpeptidase.[5] In his conclusion the author of this work, Ohlsen of the Carlsberg Laboratories, with what we consider a remarkable degree of foresight, expressed the hope that his work might sometime in the future be of help "to those who are concerned . . . with the elucidation of the problem of pernicious anæmia".

Dr. Glass's last two questions are based upon results obtained on absorption of crystalline vitamin B_{12} under certain conditions. As far as we know, there is no evidence that the pure crystalline vitamin ever occurs *as such*, either in Nature or at any stage of digestion or absorption. Until there is evidence to the contrary, such experiments cannot be regarded as physiological, and have little validity, as far as we can see, in the pathology of pernicious anæmia. We have more to say about this in our next paper and perhaps we may be forgiven if we do not enlarge on it here.

Finally, we would like to congratulate Dr. Glass on the superb paper which he read last month at the International Hæmatological Congress in Rome. We well remember his conclusion—which was not seriously challenged—that whether the intrinsic factor exists or not, no-one has found it yet. That is a sentiment we both endorse.

St. Helens Hospital,
St. Helens, Lancashire.

F. S. MOONEY
J. G. HEATHCOTE.

COLOUR INDEX IN NORMAL SUBJECTS

SIR,—Dr. Horsfield (Sept. 27) takes me to task for reporting colour-index figures to two places of decimals (Sept. 13), thereby implying an accuracy which is, to him, "without meaning".

When any measurement is reported to a certain number of significant figures it is not usually intended that the recipient of the report should assume that if the measurement were repeated exactly the same figure would be obtained. Thus it is usual to weigh patients to the nearest pound, but everyone knows that a large meal or an act of excretion could cause a change of several pounds, and no misunderstanding arises. What is important with all quantitative hospital laboratory investigations is that the nature and extent of the errors involved should be clearly understood by all concerned, and it is here that Dr. Horsfield seems to be in some confusion. He quotes the finding of Biggs and Allington that successive hæmoglobin estimations on the same subject have a standard deviation of 4·5% and apparently thinks that this figure is applicable to my work on the errors of colour-index determination.

The sampling error in hæmoglobin estimation is not the same thing as the technical error. Biggs and Allington showed that when successive hæmoglobin estimations were made on the same sample of blood the standard deviation was 1·6%. When estimations are carried out on different samples of blood from the same subject there is a much greater variation, presumably due to fluctuations in the total plasma-volume and to uneven distribution of red cells throughout the circulating blood mass. These sources of error are, however, irrelevant when one is considering the ratio of two hæmatological measurements carried out on the same sample of blood. In the present instance, if the colour-index figures had been reported to one place of decimals instead of two the result would have been to add an error of up to 5% to a measurement which has a technical coefficient of variation of about 3%.

Sir William Dunn School of Pathology,
University of Oxford.

J. C. F. POOLE.

SHORTAGE OF JUNIOR HOSPITAL STAFF

SIR,—As someone who has recently worked both in my teaching hospital and in a few peripheral hospitals I should like to comment on this subject.

There are probably three main reasons why a newly qualified graduate applies for a post at his teaching hospital, assuming he wants to: (1) the prestige he gains if he is a budding specialist; (2) the fact that he feels that it is expected of him by many; and (3) the undoubted glamour associated with the post.

When it comes to the responsibility for the overall management of clinical material, however, the preregistration houseman is far better placed in the peripheral hospital, where he has a wide selection of cases and where he is frequently "on his own". At the teaching hospital the houseman is often no more than a glorified clinical assistant carrying out the instructions of his immediate superiors, the S.H.O. and R.M.O.

Should teaching hospital posts be entirely post-registration, however, then the junior staff would miss what undoubtedly one does miss in a peripheral hospital, the stricter discipline in the work which is bound to make for a higher standard of care.

Other advantages in a peripheral hospital include the better off-duty hours (despite Mr. Howorth's proposed advertisement in his letter last week). One is usually sure of two or three evenings free each week and two weekends a month off duty. In the teaching hospital, through pressure of work, one was thankful for a half-day each week and a weekend in four.

As to why junior staff are loth to go "up country" there are obviously many reasons. Should he wish to specialise he finds himself unable to attend lectures at the medical school and medical libraries, on account of distance alone. Most consultants are very willing to help on matters of factual advice, but the more "high-powered" knowledge required for postgraduate examinations can often only be obtained at the teaching hospital.

There are many frustrations during the routine day-to-day work (e.g., poor equipment and insufficient nursing staff to carry out instructions). One cannot help noticing that, in the two types of hospitals, the attitude of the non-medical staff is markedly different. In the periphery the lay staff seem to have no idea of the relative importance of medical requirements. Junior staff who work in this continual frustration soon find that they are only too glad to get away from this atmosphere and back into the teaching hospital.

The system could be improved if an optional maximum of six months were allowed to a preregistration man

3. Glass, G. B. J. *Gastroenterology*, 1956, **30**, 37.
4. Pedersen, J., Lund, J., Ohlsen, A. S., Kristensen, H. P. O. *Lancet*, 1957, i, 448.
5. Ohlsen, A. S. *C.R. Lab. Carlsberg*, 1941, **23**.

at a teaching hospital. To encourage applicants to the peripheral hospitals there should be more facilities for study and reference, in the shape of a small medical library at the main hospital in each management-committee area, containing the recognised textbooks and journals covering subjects relevant to the various departments in the hospital; and there should be a general improvement in the equipment. Residents should be able to attend area lectures, preferably at times other than normal off-duty.

Rawtenstall, Lancashire. I. W. MANSON.

SIR,—In your last issue Mr. R. G. Henderson suggests that young doctors should be prevented from going to work abroad until hospitals in this country are adequately supplied with junior staff. Such a scheme would be very convenient for those who have no desire to see additional consultant posts created, and for consultants who wish to devote themselves to private work, but it would not be very popular with registrars. For these it would mean working in a dead-end job until the age of perhaps 40 and then being forced, for the most part, to emigrate or leave clinical medicine altogether.

If the hospital service is to provide a career for a reasonable proportion of those who embark on it, the number of middle-grade posts must be considerably reduced. There should be no registrar posts at peripheral hospitals.

Ashford Hospital, Ashford, Middlesex. M. J. D. NEWMAN.

Obituary

HENRY WALLACE-JONES

M.D., M.Sc. Lpool, F.R.C.P.

Dr. Henry Wallace-Jones, formerly senior honorary physician to the Liverpool Royal Infirmary, died in Johannesburg on Oct. 15, at the age of 70.

The son of Dr. Henry Jones, he was born and brought up in Liverpool, being educated at Liverpool College and the university, where in 1910 he graduated B.SC. in physiology with first-class honours after studying under Sherrington—an experience which later enriched his outlook as a cardiologist. He proceeded to the M.SC. in 1911 and qualified M.R.C.S. in 1912. The following year he graduated M.B. with first-class honours and he took the M.D. a year later.

In the 1914–18 war he served with the R.A.M.C., joining the British Expeditionary Force in France with the Liverpool Mobile Hospital. He was later pathologist to the Liverpool Merchants' Hospital in France. After returning to England he was appointed to the honorary staff of Liverpool Royal Infirmary, later becoming physician in charge of the cardiology department. In 1921 he took the M.R.C.P., and he was elected to the fellowship in 1930. In 1947 he served as president of the Liverpool Medical Institution. He retired the following year. His retirement was spent mainly in South Africa; but he never severed his Liverpool associations, and he returned to the city periodically—the last time only two months ago.

R. C. writes:

"Wallace was one of those warm personalities who never grew old. Some who did not know him well might have thought him casual and easy-going; the truth was that he had an inner serenity which stopped him from unnecessary fussing and from any uneasy ambition to be in the limelight. He had an alert, keen, and first-class brain, and was a physician of the highest order. Though his main interest was eventually in cardiology he was never an exclusive specialist, and he always remained a general physician, at home in all branches of medicine. He was not only a shrewd and wise clinician; he was also the kindest of men, and much beloved by his students and his patients. His students, housemen, and registrars were made to feel that they were his family, past, present, and to come; and the large number of his 'young men' who could thank his training and encouragement for their eventual appointment to positions of responsibility and honour gave him deep and solid pleasure. He could feel proud of them—and did. It will be clear that he was a fine teacher; and he was as keen on the teaching of nurses as of medical students.

"When his loyalty or his convictions were engaged, this quiet, goodhumoured man could be uncompromising; and this honest strength was not the least of his gifts to the Liverpool Royal Infirmary, which he served so long.

"When the time came for his retirement from hospital, it was typical of his vigour of outlook that he should start a new life in South Africa, where he found plenty to occupy his energies, both as a physician and as a man. He and his wife used to return periodically to Liverpool, largely in order to keep in personal touch with their many friends here; indeed it is only a short time since Wallace was among us, on one of these visits, looking as fit and as cheerful as ever."

Dr. Wallace-Jones is survived by his wife and by three sons, one of whom is a radiologist in Liverpool.

JANE TURNBULL

C.B.E., M.D. Lond.

AMONG the triumphs of State medicine in the present century the reduction of maternal and infantile mortality and the organisation for the welfare of mothers and children have been conspicuous. The pioneers who laboured in this field included Dr. Jane Turnbull.

Jane Holland Turnbull was the daughter of Lieut.-colonel Archibald Turnbull, Indian Army Veterinary Service. She was educated at Edinburgh and Reading, and studied medicine at the Royal Free Hospital School of Medicine for Women, qualifying M.B. London with first-class honours in 1899 and proceeding to M.D. in 1904. She was anæsthetist and lecturer on anæsthesia at her hospital, and was subsequently on the honorary staff of the Elizabeth Garrett Anderson Hospital and the South London Hospital for Women. During the 1914–18 war she was controller of medical services, Queen Mary's Army Auxiliary Corps. For her war services she was appointed C.B.E.

Dr. Turnbull was appointed a medical officer of the newly established Ministry of Health in 1919, and of her subsequent career A. MacN. writes:

"With a wide knowledge of obstetrics and gynæcology and much experience in administration, Dr. Turnbull was an acquisition to the medical staff of the Ministry. For ten years she was chiefly occupied in the inspection of maternity and child-welfare work. Her visits to various parts of the country were always welcomed by the medical officers of local authorities, who reaped much benefit from her tactful advice and wisdom. These gifts were especially valued by her immediate chief, Dame Janet Campbell, to whom she became deputy senior medical officer in 1929. In 1933, on Dame Janet's retirement, Dr. Turnbull was put in charge of the maternity and child-welfare division, in which capacity she well maintained the high standard set by her predecessor. An important feature of her work at this time was participation in the comprehensive special investigation into maternal mortality in England, the report on which was published as a white-paper in April, 1937. It became evident at an early stage in the inquiry that an important factor in maternal mortality was the standard of midwifery practice, both domiciliary and institutional. This finding led without delay to the Midwives Act, 1936, which provided a salaried domiciliary service of trained midwives throughout the country. In the establishing of this service and its development by local authorities Dr. Turnbull was most helpful.

"Dr. Turnbull retired from the Ministry in 1936. She lived first at her pleasant house at Princes Risborough, cultivating and enjoying the flowers in her garden. Here she was always pleased to see her friends. In her later years she lived at Queen Anne Street, London.

"In her days at the Ministry of Health, Dr. Turnbull was brisk and alert, of a kind disposition, methodical and careful in her administration, and a delightful professional colleague. She thought for others and could always see the other person's point of view—a most persuasive gift in the discussion of controversial questions. She never sought the limelight, and much of her work which is of permanent value must remain unchronicled. It was wrought by an accomplished woman who dedicated her talents to the welfare of women and children. Hers was a full and well-spent life."

Dr. Turnbull died at Canterbury on Oct. 15 at the age of 87.

JAMES WATT

M.A., M.D. Aberd., D.P.H.

Dr. James Watt, who died on Oct. 4 at the age of 74, will be remembered as an outstanding figure in tuberculosis from before the 1914–18 war until his retirement in 1948.

He graduated M.B. with first-class honours at Aberdeen in 1908. After studying in Germany, he held the post of senior medical officer at the Royal National Hospital, Ventnor, until 1916 when he entered the service of what was then the Metropolitan Asylums Board as medical superintendent of the Downs Sanatorium, Sutton, becoming chief medical officer of the tuberculosis service of the Board. Also in 1916, he graduated M.D. with highest honours. In 1922 he became the first medical superintendent of the new King George V Sanatorium, Godalming (at first Highdown Sanatorium)—a post which he held until his retirement. Though pre-eminently associated with the development of this hospital, in which his interest was profound, his influence spread far beyond it. He was a leading member of the Society of Superintendents of Tuberculosis Institutions and its successor, the Tuberculosis Association (now the British Tuberculosis Association), and for many years sat on the Joint Tuberculosis Council, of which he was at one time chairman. In the 1920s his interest in the status of those nursing in tuberculosis caused him to struggle for their recognition on a special register. Moreover, he was a pioneer in the scheme by which nurses who themselves had had tuberculosis could be rehabilitated and specially trained on the staffs of sanatoria.

A colleague, J. V. H., writes:

"Though he was a sound clinician, James Watt will be perhaps remembered professionally as a first-class administrator. He was the type of medical superintendent which not seldom in the past emerged within the framework of the larger local authority, well taught and meticulous in all the details of administration, loyal both to his employers and his staff, uncannily knowledgeable about all, or nearly all, that went on in his 'parish'. His tall rather dominant figure was softened by a Scots sense of humour, by the obvious integrity of his character, and by his eager interest in people and things. His experience and common sense made him an invaluable committee-man, as those who worked with him in the L.C.C. and on the J.T.C. will always remember.

"Apart from his work, Dr. Watt's great interest was his garden. His two gardens, that at King George V Sanatorium and the much smaller one which he had on retirement, both showed how much love and knowledge he had brought to their care. The years of his retirement were marred by a serious road accident, following which he suffered from increasing ill health which he bore with great courage."

Dr. Watt is survived by his wife and son and daughter.

A memorial service is to be held at King George V Hospital, Godalming, at 11 A.M. on Saturday, Nov. 8.

Notes and News

THE MANSON ORATION

"THERE are many bad doctors in the world but very few good ornithologists," said Alfred Newton, F.R.S., at Cambridge to the young Philip Bahr. "You cannot serve God *and* Mammon," said his father-in-law, Sir Patrick Manson (and by Mammon he meant the birds). When Sir Philip Manson-Bahr gave the first Manson oration last week before the Royal Society of Tropical Medicine, a stuffed Ceylon jungle-fowl (shot by Sir Patrick), which lay on the table before him, seemed to symbolise what might have been; but all who heard his account of the March of Tropical Medicine during Fifty Years must have been glad that ornithology did not win the day.

Picturesque and wholly characteristic, his long and fascinating narrative began in 1908 at the London School of Tropical Medicine, under the spell of Patrick Manson, "the greatest teacher I have known". In the hospital there would be 12–14 cases of beriberi—a number no longer to be seen together anywhere in the world. From London, with his wife (Manson's daughter), he went to Fiji, setting up headquarters in a primitive house soon to be wrecked by a hurricane. There he worked with Mr. W. J. Muggleton (still his assistant, collaborator, and friend) on bacillary dysentery and filariasis. He isolated Shiga's bacillus from the housefly, and, unaware of an earlier German report, described the macrophages that have so often been mistaken for *Entamœba histolytica*—sometimes with disastrous results, as in Gallipoli, where thousands of cases of bacillary dysentery were misdiagnosed and erroneously treated with emetine. Studying filariæ, he extracted these worms from the epitrochlear glands of patients, and was disappointed not to find them in his own epitrochlear glands after he had induced half a dozen larvæ to pass through the skin of his hand. He displayed the mummified remains of worms blocking lymph-vessels; and he found that artificially infected *Aedes pseudoscutellaris* mosquitoes could contain a load of as many as 48 larvæ, though he failed to find their breeding-place in the damaged shells at the tops of coconut trees. This mosquito proved to be the most important insect in the Pacific.

In Ceylon he travelled thousands of miles with his diagnostic equipment on a bicycle. Sprue proved an enigma—which it still is. Manson, as a visitor, stimulated research on filariasis and malaria, and "made a fool of us every day in the laboratory". It was Manson, too, who sent Muggleton to Sir Arthur Shipley at Cambridge, and his son-in-law to the British Museum, to study snails, which he felt sure must be the intermediate hosts of bilharzia. But the war intervened, and Captain Bahr, in Egypt with his microscope and little other equipment, was immersed in the problem of dysentery from the Dardanelles and the differentiation of every kind of disease. In 1917, on the advance into Palestine, where Colonel Johnston Abraham was his medical chief, his indiscretion in sketching out of doors while the G.O.C. was passing led to an encounter in which Lord Allenby (a fellow ornithologist) accepted the idea of malaria diagnostic units (one for each of the army's six divisions) and told his staff to "give this officer all he asks for". After a 6-week course for the personnel, these units were established, and they examined 40,000 blood slides during the advance. There were 12,000 cases of malaria with 700 deaths; but this, Sir Philip thought, was a cheap price: "I don't know what would have happened otherwise." Pellagra was another problem—he saw 925 cases in prisoners—and cholera in Egypt in 1918. He recalled how one day in the desert he saw an approaching line of 25 camels, each bearing, for his examination, a load of stools: they had come from Beersheba, 5 days' journey distant, at a temperature of 105°F!

Recalling that W. E. Dixon, his teacher at Cambridge, said that only three drugs were useful for tropical diseases—mercury for yaws, quinine for malaria, and ipecacuanha for amœbiasis—Sir Philip concluded with some of his experiences of the early trials, and startling victories, of 'Bayer 205' in trypanosomiasis, 'Plasmochin' (pamaquine) and 'Atebrin' (mepacrine) in malaria, 'Prontosil' in endocarditis and abortus

fever, sulphetrone in leprosy, nicotinic acid in pellagra, and folic acid in sprue. In these fifty years almost all the chief scourges of the tropics had been conquered—potentially conquered, he might have said—and he had evidently found the half-century exciting. But excitement, like beauty, is something people often have to find for themselves; and Sir Philip is one of those whose life would have been interesting in any period and any place.

A PICTURE OF THE N.H.S.

THE B.B.C. television documentary, *On Call to a Nation*, which was to be seen last Wednesday, was an impressive attempt to portray the National Health Service as doctors see it, ten years after its inception. Mr. Richard Cawston, who wrote and produced the programme, is to be congratulated on so very nearly bringing off the impossible; for it *is* impossible to compress into a 75-minute film a picture so well balanced that it will satisfy all doctors in the N.H.S. and still achieve its prime aim of interesting people in simple terms and making them think. As a lifelike account of what doctors do in the service, the film seldom faltered; and it gave an encouraging impression of many doctors trying their best to iron out the difficulties as they see them and make the service increasingly efficient.

The 25 doctors who pronounced on different matters from time to time succeeded in bringing out most of the more substantial criticisms to which the N.H.S. is prone; but Mr. Cawston had skilfully seen to it that his film did not lapse into a long moan, and his touch was lively and constructive. One point, however, where criticism seemed to weigh too heavily, without an appropriate counterbalance, was in certain passages concerned with the work of public-health departments. Local-authority clinics were roundly condemned by two general practitioners, and the contrary arguments were not given an effective hearing. The portrait of hospital outpatients was a little grim, perhaps; and one of the illustrative cases, about which a familiar figure was seen dictating at the end of an outpatient session, will connect anæmia with cancer in many viewers' minds in a way that could cause needless anxiety.

These reservations apart, the film did very well, particularly in the sequences on general practice. Doctors who saw it will have been reminded of the other man's headaches, and that is always a healthful process.

MEDICAL FILMS

Two new films of interest to obstetricians have been made with the collaboration of Prof. W. C. W. Nixon at University College Hospital, London.

The Routine Use of Ergometrine in the Third Stage of Labour (16 mm., sound, colour, 7 minutes, Great Britain, 1958) is a plea by Professor Nixon that the drug should be administered in all deliveries as soon as the head of the child appears. Referring to the introduction of ergometrine into clinical practice by Professor Chassar Moir in 1935, he states that it fell into ill repute as it was used too late on exsanguinated patients. A midwife is then seen delivering two patients, one in the lithotomy position and the other in the left lateral position; and in both cases 0·5 mg. ergometrine is injected intramuscularly as soon as the head is delivered. Professor Nixon states that a contraction is produced in four minutes and adds: "the provision of another syringe is a small price to pay for the reduction of deaths from postpartum hæmorrhage".

The Management of Twins in Pregnancy and Labour (16 mm., sound, colour, 21 minutes, Great Britain, 1958) shows the diagnosis and delivery of twins and the complications that may occur. It is emphasised that, as twinning is an abnormality, further abnormalities may be encountered; so the confinement must take place in hospital. The differences between monozygotic and dizygotic twins are demonstrated and shown on diagrams. Then the diagnosis and complications of twins are enumerated and various lies shown diagrammatically. The remaining two-thirds of the film is devoted to the delivery of two sets of twins, the first being uncomplicated vertex presentations, the second being complicated by uterine inertia necessitating forceps delivery under general anæsthesia. In this case the first child was a vertex presentation, and the second was a shoulder which was converted to a breech by internal version. The film is too long but includes much useful teaching material.

Both films may be obtained free of charge from the Wellcome Film Library, 183, Euston Road, London, N.W.1.

WORKSHOP FOR THE DISABLED

THE London County Council has set up in St. Pancras an experimental workshop for the training and reablement of severely handicapped men.

The workshop was designed by the L.C.C.'s architect with plenty of light, space, and air, and has cost £25,000 to build. There is room for some 35 handicapped men (including 5 "unemployables", for whom there has so far been no opportunity for training). Covered parking-space has been provided for wheelchairs and motorised tricycles. Equipment includes a saw bench, dimension saw-planner, band-saw, and thicknessing, sanding, drilling, and mortising machines. Each worker has his own tool kit. It is hoped later to open a hostel for workers next door to the workshop. The 30 men who have already joined the workshop include epileptics, paraplegics, deaf mutes, and poliomyelitis patients. 18 (including 1 "unemployable") have already passed a three-month wood-machining or cabinet-making course and are now regularly employed at the workshop. Eventually it is hoped to settle many of these workers in normal employment.

The Ministry of Labour and National Service pays allowances (ranging from £4 19*s.* to £6 10*s.*) and fares for trainees. The rate of pay (£7 3*s.*) and employment conditions of workers who have passed the course are the same as those negotiated between Remploy Ltd. and the trade-unions. Employees work a 44-hour five-day week. Subject to a maximum of 10*s.* a week each worker is reimbursed travelling expenses in excess of 6*d.* a day. A deficiency grant of 75% of the approved net cost of the workshop is to be made by the Ministry of Labour and National Service to a maximum of £150 a year for each worker recommended.

University of London

At recent examinations the following were successful:

D.C.P.—Fatima Sughra Ahmed, Mirghani Yousif Ali, E. F. Bowers, Robert Carroll, Betty M. Clark, Casparus Hendrik Coetzee, D. M. Gomez, J. W. Hill, D. O'B. Hourihane, M. S. Israel, E. B. La'Brooy, Ma Than Myint, T. K. Narayanan, Nadarajah Parameshwaran, Leo Sefton, J. M. Uku, H. I. Williams.

The following degrees have been conferred:

M.D.—Edward Parry-Jones, L. S. Sacker.
M.S.—M. A. Birnstingl.

University of Liverpool

The McMurray lecture in orthopædic surgery will be given by Prof. Walter P. Blount, head of the department of orthopædic surgery, Marquette University, Wisconsin, on Friday, Nov. 7, at 5.15 P.M., in the New Medical School. He will speak on Fractures in Children.

University of Sheffield

Dr. Helen Beladi has been appointed research assistant in virus diseases and Dr. Parijat Chowdhuri research assistant in the department of obstetrics and gynæcology.

University of Aberdeen

Dr. J. L. Malcolm, a member of the staff of the National Institute for Medical Research, has been appointed to the regius chair of physiology in succession to Prof. E. W. H. Cruickshank, who has retired.

Dr. Malcolm studied medicine at the University of Otago and graduated B.MED.SC. in 1935. While holding a demonstratorship in the department of physiology at Otago he went on to take his M.B. in 1938. Two years later he was appointed assistant lecturer in the department of public health, and the following year senior lecturer in experimental physiology, at the Otago Medical School. In 1948, he came to London as the first of a series of exchanges arranged between the school and St. Thomas's Hospital, and in 1949 he was appointed to the readership in physiology at St. Mary's Hospital Medical School. After a year as visiting professor at the New York State University in Brooklyn in 1953, he joined the staff of the M.R.C., where he has taken part in studies of the action of 5-hydroxytryptamine and *d*-tubocurarine on the central nervous system.

Royal College of Physicians of London

On Thursday, Nov. 6, at 5 P.M. at the college, Pall Mall East, S.W.1, Dr. K. W. Donald will give the Bradshaw lecture on heart disease and exercise.

Conference on Orthopædics in Glasgow

This conference, arranged by the University of Glasgow and the Royal Faculty of Physicians and Surgeons, will be held at the Faculty, 242, St. Vincent Street, Glasgow, C.2, from Nov. 17 to 21.

Royal Commission on Doctors' and Dentists' Remuneration

The Royal Commission will hold a public hearing on Friday, Oct. 31, at 10, Carlton House Terrace, London, S.W.1. Representatives of the Joint Consultants Committee have been invited to attend. The hearing will begin at 11 A.M. and will, if necessary, be continued into the afternoon.

College of General Practitioners

Midland Faculty.—The college has arranged with the staffs of Worcester Royal Infirmary and Powick Hospital for six medical meetings to take place this autumn. The first will be held on Thursday, Nov. 6, at 3.30 P.M., at Worcester Royal Infirmary, when Dr. J. A. Pridham will speak on the World Medical Association, its history, aims, and activities. Further particulars may be had from Dr. A. J. Laidlaw, 29, Barbourne Road, Worcester.

Northern Home Counties Faculty.—On Tuesday, Dec. 2, at 8 P.M., at the White Hart Hotel, St. Albans, Dr. Thomas Parkinson will give a lecture on chest pain.

A New Kind of Hostel

The trustees of the London Parochial Charities have set aside £50,000 to be spent over five years, to set up two hostels where children leaving schools for the educationally subnormal will be helped to find their place in the community. At the invitation of the trustees, the National Association for Mental Health agreed to be responsible for the experiment, and the first hostel, which is to be for boys, will be opened on Oct. 30 at Blackheath.

The second of the hostels will be for girls. Each will accommodate 20–30 school-leavers. The boys and girls will first be settled in suitable employment and permanent accommodation will later be found for them.

The Wellcome Trust

The Wellcome Trustees have announced that grants made during the half-year ended Aug. 31 included:

Postgraduate Medical School of London.—Up to £60,000 for the cost of including a Wellcome research library in the proposed new buildings.

Institute of Psychiatry, Maudsley Hospital.—Up to £37,000 to provide laboratories in which integrated research by the departments of neuro-endocrinology and neuropathology may be carried out.

Department of anatomy, University of Birmingham —Up to £36,500 to extend the research laboratories and animal accommodation.

Department of zoology, University of Edinburgh.—Up to £25,000 to provide additional research accommodation.

University of Western Australia.—£50,000 to endow a Wellcome research department of pharmacology.

Institute of Medical Research, North Shore Hospital of Sydney, Australia. —Up to £17,000 to build and equip laboratories for experimental medicine and surgery.

Electron microscopes on loan.—£34,000 to buy three electron microscopes, which will be placed on indefinite loan with the biophysics research unit of the Medical Research Council, King's College, London, the Sir William Dunn School of Pathology, University of Oxford, and the London School of Hygiene and Tropical Medicine.

Dr. Anne N. M. Brittain has been appointed a deputy medical commissioner of the General Board of Control for Scotland.

Dr. Doreen Vermeulen-Cranch, F.F.A. R.C.S., has been appointed the first professor of anæsthesiology in the University of Amsterdam.

Appointments

ASTON, J. N., M.B. Lond., F.R.C.S.: surgeon, orthopædic department, St. Bartholomew's Hospital, London.

HOARE, E. D., M.D. Cantab.: director of the department of clinical pathology, London Clinic.

JELINEK, GUSTAV, M.D. Prague: part-time S.H.M.O., department of venereal diseases, St. Bartholomew's Hospital, London.

JOHNSTON, JOHN, L.R.C.P., D.P.M.: consultant psychiatrist and physician-superintendent, Broadgate Hospital, Beverley, Yorkshire.

MUCHO, W. A., M.D. Warsaw: senior assistant psychiatrist, Towers Hospital, Leicester.

STUART, PETER, M.B. Glasg., F.F.A. R.C.S., D.A.: consultant anæsthetist, East Cumberland group of hospitals.

South Western Regional Hospital Board:

ISAAC, D. H., M.D. Lond., M.R.C.P.: consultant physician-geriatrician, South Somerset clinical area.

MCCARTHY, T. F., M.D. Wales, M.R.C.P.E.: assistant geriatrician, North Gloucestershire clinical area.

SLADE, NORMAN, M.B. Brist., F.R.C.S.: consultant genitourinary surgeon, Bristol clinical area.

Alcoholism a Disease and a Challenge

The Temperance Council of the Christian Churches are holding a conference on this subject at Church House, London, S.W.1, on Monday, Nov. 3. The speakers will include Dr. Basil Merriman and Dr. Lincoln Williams. Tickets (7*s.* 6*d.* for one session and 12*s.* for two sessions) may be had from the Rev. Dr. T. G. Dunning at the council, Parliament Mansions, S.W.1.

Diary of the Week

OCT. 26 TO NOV. 1

Monday, 27th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
4 P.M. Dr. Brian Ackner: Psychiatric Aspects of Termination of Pregnancy.

INSTITUTE OF CHILD HEALTH, HOSPITAL FOR SICK CHILDREN, Great Ormond Street, W.C.1
5 P.M. Prof. Ihsan Dogramaci (Ankara): Malnutrition in Infancy and its Management.

MANCHESTER MEDICAL SOCIETY
9 P.M. (The Medical School, University of Manchester.) *General Practice.* Prof. Stanley Alstead: Medical Truants.

Tuesday, 28th

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. G. S. Wilson: Infectious Enteritis.

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Medicine.* Dr. A. H. Douthwaite: Development of the Treatment of Duodenal Ulcer. (Presidential address.)

ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Mr. David Currie: The Miracle of Childbirth.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. G. C. Wells: Dermal Connective Tissue.

ROYAL STATISTICAL SOCIETY
5.30 P.M. (London School of Hygiene and Tropical Medicine.) *Medical Section.* Dr. O. M. Lidwell, Dr. R. E. O. Williams: Effect of Various Factors on the Incidence of the Common Cold.

Wednesday, 29th

POSTGRADUATE MEDICAL SCHOOL
2 P.M. Dr. Paul Fourman: Magnesium Metabolism.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Ringworm Infections.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. F. H. Scadding: Mode of Presentation of Carcinoma of the Bronchus.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Dr. Annie Sydenham: Maternity and Child Welfare Work in a Hong Kong Mission Hospital.

OXFORD UNIVERSITY
5 P.M. (Radcliffe Infirmary.) Dr. W. G. Spector: Role of Endogenous Mechanisms in Acute Inflammation. (Litchfield lecture.)

UNIVERSITY OF LIVERPOOL
4.45 P.M. (New Medical School, Ashton Street, Liverpool.) Sir Gordon Gordon-Taylor: The Incomputable Factor in Cancer Prognosis. (William Mitchell Banks lecture.)

Thursday, 30th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Sir John McNee: Barber-Surgeons in Great Britain and Ireland. (Thomas Vicary lecture.)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. R. E. O. Williams: Epidemic Staphylococcal Infection in Hospitals.

INSTITUTE OF PSYCHIATRY, The Maudsley Hospital, Denmark Hill, S.E.5
5 P.M. Prof. P. M. Daniel: Experimental Approaches to Neuropathology. (Inaugural lecture.)

ASSOCIATION OF ANÆSTHETISTS OF GREAT BRITAIN AND IRELAND
9 A.M. (Southport.) Opening of three-day meeting.

HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh.) Prof. A. G. R. Lowdon: Emergency Re-operations in Abdominal Surgery.

UNIVERSITY OF ST. ANDREWS, DUNDEE
5 P.M. Mr. Hedley Atkins: The Three Pillars of Clinical Research.

Friday, 31st

ROYAL SOCIETY OF MEDICINE
10.30 A.M. All-day symposium on Disorders of the Small Intestine. (Speakers: Dr. E. N. Rowlands, Dr. B. C. Morson, Dr. Margot Shiner, Dr. Frank Pygott, Mr. Thomas Dormandy, Mr. A. N. Smith, Dr. W. I. Card, Mr. J. M. Pullan, Dr. Avery Jones, Prof. John Bruce.)

POSTGRADUATE MEDICAL SCHOOL
10 A.M. Prof. P. A. Fitzgerald: Adrenal Surgery.
4 P.M. Dr. E. N. Chamberlain: Rheumatic Carditis.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Miss Edith Whetnall: Advances in the Use of Hearing Aids.
5.30 P.M. Dr. T. V. L. Crichlow: Œsophageal Problems.

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES, 11, Chandos Street, W.1
7 P.M. Dr. B. F. Reeves: Variations in the Leucocyte Content of the Cervical Secretions. Dr. J. H. Eckersley, Dr. Jack Barrow: Locan Pessaries in the Treatment of Trichomonas Vaginitis.

ST. MARY'S HOSPITALS, Manchester
4.30 P.M. (Clinical Sciences Building, York Place, Manchester, 13.) Prof. A. M. Claye: The Teaching of Obstetrics—New Edition. (Lloyd Roberts lecture.)

PLYMOUTH MEDICAL SOCIETY
8.30 P.M. (Freedom Fields.) Dr. A. E. Clark-Kennedy: The Right to Die.